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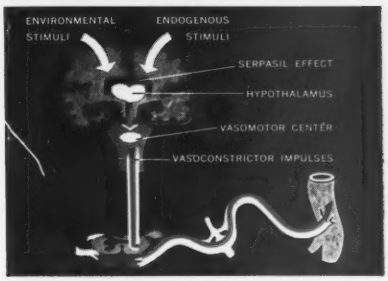

Adapted from Moyer, J. H., Dennis, E., and Ford, R.: Arch. Int. Med. 96:530 (Oct.) 1955.

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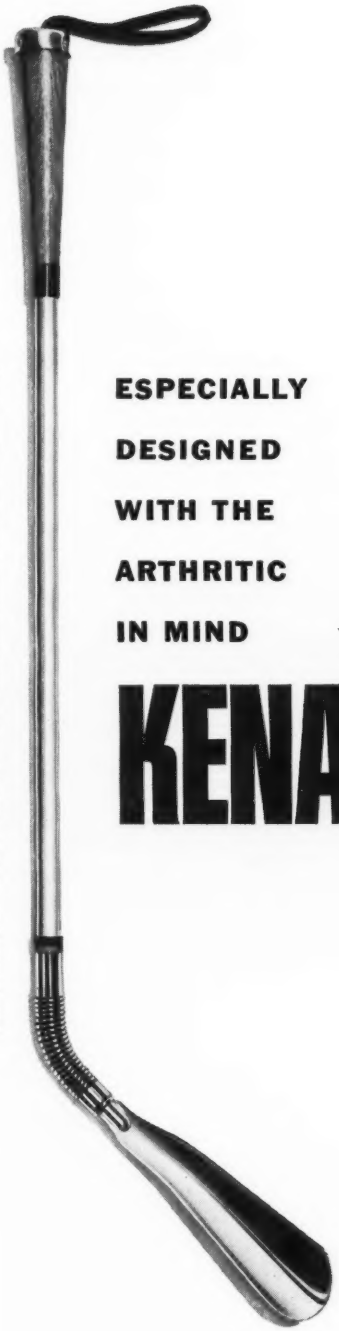

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Editorial

On the Selection of Patients for Surgical Repair in Congenital Defects

THE remarkable advances in medicine and surgery bring a new responsibility to the physician. Furthermore, the philosophy of the patient and of the parents has entirely changed. Fear of experimentation has been replaced by a passion for some "new" treatment. Most persons with any sort of cardiac abnormality at the present time are tremendously anxious for surgery. They hear of the extraordinary success. The dark sorrow of the background that makes the successes stand out so brilliantly is not known or is overlooked. Even though no physician wishes to withhold the benefit of surgery from his patient, nevertheless operation is not always possible. Furthermore, in many instances the risk involved is too great and the amount to be gained too slight to justify operation. Therefore, it behooves the physician to review with his patient that person's particular problem in order to give him the best possible advice.

Although every patient must be considered individually, certain broad principles are applicable to all. First, is the condition operable? Second, what is the risk of the operation? What is the mortality rate and what are the possible complications? Third, what are the chances that surgery will be successful? Fourth, how much benefit can be expected from successful surgery? Fifth, how great is the patient's incapacity? Sixth, what is the prognosis without operation? Finally, what is the optimal age for operation? What is the danger of and what is to be gained by waiting? Will postponement of the operation decrease or increase the risk of surgery? Such are the questions we should consider.

If the risk of operation is slight and the gain is great, as for example, the restoration of the circulation to normal by the closure of a patent ductus, operation is usually indicated. If the risk is slight but the gain is relief from strain, as in pure pulmonary stenosis where after operation the pulmonary valves remain abnormal, there must be evidence of demonstrable strain for the operation to be indicated.

If, however, the risk is great, then the gain must be great or the immediate prognosis without surgery extremely poor for operation to be indicated. If the patient's condition is critical or hopeless without operation, a great risk can be taken for a moderate gain. Nevertheless, unless the patient is severely incapacitated, even a moderate risk is seldom indicated for a minimal gain. Furthermore, it is seldom if ever justified to take a great risk for a doubtful gain.

For the correct assessment of these factors, accurate diagnosis of the nature of the malformation is essential. Indeed, the importance of accurate clinical diagnosis prior to surgery cannot be too strongly stressed. In the first place, accurate diagnosis is essential in order to determine prognosis. Secondly, it is essential in order to determine both the risk of operation and the amount to be gained from operation. Finally, it is necessary in order to determine the nature of the operation

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and also the location of the incision. Can the operation be performed by a simple thoracotomy? Is hypothermia necessary? Is open heart surgery with a pump and oxygenator necessary?

Although the surgeon can check a number of points at the time of surgery, it is seldom possible to make an accurate diagnosis by the external examination of a beating heart through a chest incision. It is a grave mistake to open the heart, either the atrium or ventricle, unless it is clearly indicated.

In addition to accurate diagnosis, it is important to assess the patient's incapacity. In almost all malformations, there are all grades of severity. Some are so mild as to be compatible with a long and active life; others so severe as to cause death within the first few months of life. Therefore, each patient must be considered on an individual basis. Nevertheless, there are certain broad factors that aid in the evaluation of the problem.

The most important factors of prognostic significance are anoxemia, progressive cardiac enlargement and the rate at which enlargement occurs, and the pressure under which the blood is ejected to the lungs.

Adults die from cardiac failure or coronary insufficiency. Infants usually die from anoxemia or from cardiac failure.

Anoxemia stimulates polycythemia. Nevertheless, many infants die from anoxemia without developing polycythemia. For this reason, the degree of anoxemia is far more important than is the intensity of the cyanosis, the size of the heart, or the intensity of the murmur. Cessation of weight gain is an ominous sign. Fortunately, if a cyanotic infant who ceases to gain weight has clear lung fields, he can usually be helped by operation.

In older patients, severe anoxemia leads to polycythemia. If, however, the patient can constantly maintain an oxygen saturation of the arterial blood between 66 and 75 per cent during exercise, the tendency for polycythemia is reduced to a minimum or entirely abolished and the mild oxygen unsaturation of the arterial blood is well tolerated.

Polycythemia, although compensatory, may in itself cause difficulty. If the oxygen saturation of the arterial blood is below 66 per cent or drops below that level while the patient exercises, the patient tends to develop polycythemia; the red blood cell count, the level of the available hemoglobin, and the hematocrit tend to rise. A hematocrit level between 50 and 60 does not alter the life expectancy of the individual and even a hematocrit between 60 and 65 is well tolerated. A hematocrit over 70 is cause for concern; as it approaches 76 to 80 per cent, the danger of thromboses markedly increases. A hematocrit over 80 is dangerous. Nevertheless, will the operation correct the tendency for the patient to develop polycythemia?

Progressive cardiac enlargement is always serious and unless brought to an end, will ultimately lead to cardiac failure and death. Many malformations, however, cause an immediate increase in the size of the heart as it adjusts to the extrauterine circulation and once this adjustment has been made, further increase in the size of the heart is proportional to growth. Therefore, although progressive enlargement is always serious and necessitates close observation in early infancy, such enlargement is not always fatal. The rate of enlargement is important. If the rate is rapid, enlargement must cease or else the prognosis is poor. If, however, the enlargement comes to an end, even though the heart is enormously enlarged in infancy, the prognosis may yet be good. The heart of an infant is larger in proportion to the chest than is the heart of a child, and the heart is larger in proportion to his chest than is the heart of the adult. Indeed, many an infant may require digitalis to maintain compensation and by the time he is an adult, show only slight to moderate cardiac enlargement.

Pulmonary hypertension is serious. The lungs are not constructed to receive blood under systemic pressure. Over a period of years the abnormal pressure will lead to intimal proliferation and progressive increase in the pulmonary vascular resistance, which is irreversible. We do not know how soon such changes take place but it appears that when

the condition dates from birth, there may be a delay in the opening of the pulmonary vascular bed that protects the lungs for months and even for years. Furthermore, it apparently requires a matter of years; 4, 6 or 7, or 8 years, for irreversible changes to occur in the lungs. Mild to moderate pulmonary hypertension is well tolerated; a systolic pressure in the pulmonary artery of 30 to 40 mm. of mercury and probably 50 mm. of mercury is well tolerated; a systolic pressure of 70 to 80 mm. and a diastolic pressure of 50 mm. is cause for concern. Nevertheless, if operation is performed for this reason, it must relieve the pulmonary hypertension.

The direction of venous blood into the systemic circulation without its passage through the lungs increases the risk of a brain abscess. This risk, however, is not great (probably 1 to 2 per cent). Therefore, that in itself is only an indication for operation if the operative mortality is proportionately low.

Will the operation lessen or eliminate the risk of subacute bacterial endocarditis? If the malformation restores the circulation to normal, there is hope that correction of the malformation will lessen the risk of subacute bacterial endocarditis. The successful ligation or division of a ductus appears to eliminate the danger of subacute bacterial endocarditis as no case of subacute bacterial endocarditis has been reported over a 15-year period in a patient in whom the ductus has been successfully ligated or divided.

The above malformation is the only one in which the risk of subacute bacterial endocarditis has been virtually eliminated. It has been known to occur in a person in whom a coarctation of the aorta had been resected. It has occurred in a patient in whom valvulotomy had been performed. Patients with tetralogy of Fallot and an anastomotic procedure are still susceptible to subacute bacterial endocarditis. It remains to be seen whether a ventricular septal defect can be closed sufficiently smoothly so that there are no minor irregularities on which the bacteria can lodge. Certainly all such patients should still have prophylactic antibiotics prior to dental extractions and tonsillectomy. Indeed, the favorable reports of the elimination of subacute bacterial endocarditis in patients with patency of the ductus arteriosus have been obtained with the benefit of antimicrobial agents. Therefore, even for these patients it is wise to continue such therapy because, although curable, subacute bacterial endocarditis does injure the heart and lessen the cardiac reserve.

Will the operation lessen the patient's incapacity? And if so, how much? Occasionally, the patient's cardiac handicap is not the cause of his incapacity. On the other hand, in all malformations there appears to be a critical level above which the patient is virtually asymptomatic and below which his incapacity rapidly increases. Therefore, if the patient is close to that level, a slight improvement may give great relief. It is, however, important not to promise more than can be obtained. If there is doubt as to the extent of improvement after operation, let the patient be happily surprised.

Mental retardation and physical retardation are two separate things. If a child with a normal mentality is exhausted, his school work may be impaired. Such children may be greatly helped by operation. If, however, he is a mentally retarded child, increase in the oxygen supply to the brain will not improve his mentality. A physically strong body in a mentally weak patient is not always desirable; indeed, it is often a liability to society.

Social conditions also deserve consideration. Is the child constantly exposed to infection? Can he attend school or have a home teacher? Can he be adequately cared for while waiting for improvement in surgical technic? If an adult, is the patient married? Is he the bread winner of the family? Is she the mother of young children?

Finally, the immediate as well as the ultimate prognosis without operation must be considered. The immediate prognosis is extremely important because surgical technics for the correction of malformations are advancing rapidly. What is not operable this year may be operable next year. Further-

more, an operation that carries a high mortality rate today will carry a lower one in the future. Therefore, only those patients who are seriously incapacitated and who cannot afford to await the improvements in technic should be submitted to an operation that carries a high mortality rate. For this reason, the risk of operation at the present time must be evaluated against the risk or the advantage of waiting until a future date.

It is also important to remember that "we know not what is to come." It may yet be possible to dissolve intimal proliferation and thereby help patients with pulmonary hypertension and injury to the pulmonary vascular bed. Certain it is that with the steady advances in cardiac surgery, sterilization of a young woman is seldom indicated. Sad it is when a young woman with a correctable malformation is referred to a doctor who says, "We are glad to be able to restore your heart and circulation to normal" and she replies, "What is the use? I can no longer have a child."

Finally, it is important to remember that the extraordinary is not necessarily the serious. A patient may have an extremely bizarre malformation that is entirely compatible with longevity. Therefore, if the patient is not severely incapacitated, operation is contraindicated. Furthermore, the more complicated the malformation, the more difficult is the operation. Consequently, unless a complicated malformation is causing serious difficulty, operation is contraindicated.

Indeed, even if the condition is serious as in aortic stenosis or a high ventricular septal defect, if the patient is not seriously incapacitated, limitation of activity should usually be tried before operation is recommended. This makes the patient and the family aware of the seriousness of the condition.

Although the final decision rests with the patient, it is the physician's responsibility to guide the patient's thinking and aid him to reach a wise decision. In a very real sense, the patient's decision reflects the physician's opinion.

It is not sufficient that the patient is not afraid of operation; he should *want* it. If a patient is afraid of operation, that in itself increases the risk of operation. A patient who is "scared to death of operation" is a poor risk. If there has been great deliberation combined with opposition, the family will almost invariably feel extremely bad, possibly bitter, if the patient does not survive the operation. This fact in itself deserves consideration but it should never influence the physician to take a stand which in his heart of hearts he doubts. Furthermore, if the child who does not want operation dies at operation, the parents will feel far more responsible for the patient's death than if they knew the child wanted it. Now that we have won the confidence of the public, it is imperative never to abuse that confidence.

HELEN B. TAUSSIG

A Correlative Study of Postmortem, Electrocardiographic, and Spatial Vectorcardiographic Data in Myocardial Infarction

By G. E. Burch, M.D., L. G. Horan, M.D., Joseph Ziskind, M.D., and J. A. Cronvich, M.S.

The spatial vectorcardiograms (sVCG) and electrocardiograms were studied with respect to the gross and microscopic data in 59 instances of myocardial infarction. Besides the early abnormalities in the QRS sÊ-loop frequently associated with the electrocardiographic Q of infarction, there were recognizable alterations in the sVCG associated with the anatomic location of the infarction: lateral wall infarcts shortened vectors in mid-QRS sÊ-loop, and posterior lateral basal infarction altered the terminal portion distinctively. The myocardial lesions included fresh infarcts, solid scars, scattered fibrosis, and scar with interwoven intact muscle fibers. Where many normal-appearing fibers were present in the lesion, the previously recorded ECG or sVCG frequently failed to show the diagnostic signs of infarction. However, by presenting the depolarization complex in greater detail, the sVCG supplemented the ECG, improving the accuracy of diagnosis of infarction, especially among the smaller, less solid lesions.

FOR several years it has been postulated[1, 2] and suggested by clinical studies[3-9] that the spatial configuration of the vectorcardiogram would be altered in a predictable fashion by myocardial infarction and that these alterations would have some diagnostic significance. As theoretic considerations of electrocardiographic studies had suggested, the early portions of the QRS sÊ-loop may be visualized as spatially oriented away from the centroid of the infarcted area and toward the centroid of the heart. Previous reports[6, 9] have been based almost entirely upon clinical data; only 3 or 4 hearts[7, 8] were ever examined at necropsy, usually several weeks to years after recording of the spatial vectorcardiogram. The present investigation was undertaken 2 years ago to study the relation of the electrocardiogram (ECG) and the spatial vectorcardiogram (sVCG) to the clinical data and postmortem gross and microscopic observations in the heart regardless of the cause of death. This report is concerned mainly with the sVCG, and ECG being discussed as specifically indicated. Furthermore, spatial vectorcardiographic alterations produced by infarction that correspond to generally accepted electrocardiographic criteria of this disease are not discussed in detail; only observations of special interest are included.

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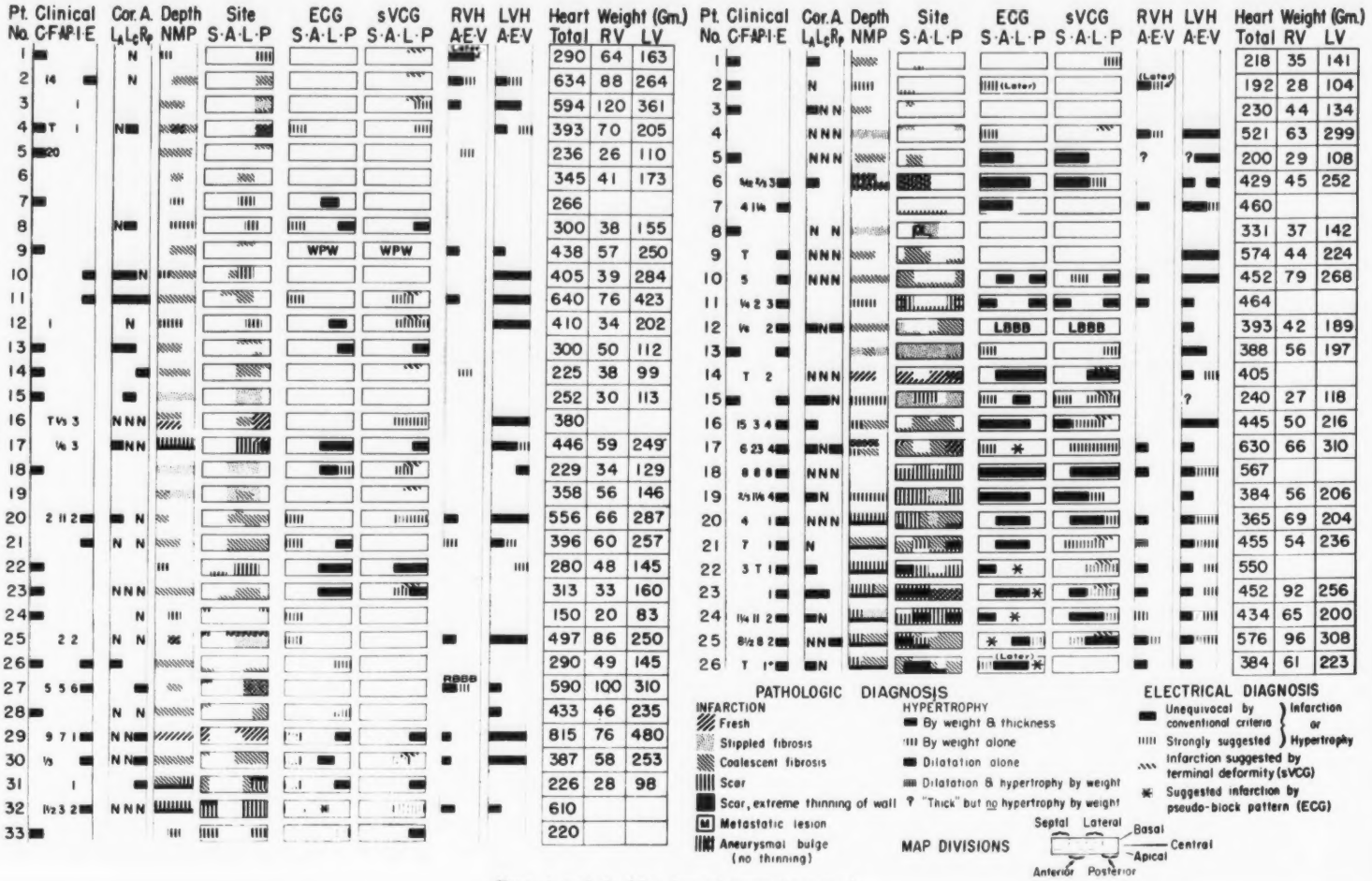
Aided by grants from the U.S. Public Health Service (H143), the Upjohn Company, Kalamazoo, Mich., and The Thibodeaux Research Foundation.

Materials and Methods

The conventional ECG and the sVCG, obtained with the equilateral tetrahedral reference frame, were recorded on patients at the Veterans Administration Hospital in New Orleans who were considered liable to die within a few days or hours. The incidence of necropsies at this Hospital is high, postmortem examinations having been obtained in about 90 per cent of the fatal cases. Fifty-nine of 160 hearts obtained for careful gross and microscopic study had one or more infarcts of the ventricular myocardium. Hearts with an occasional isolated scar of less than 5 mm. in diameter but without clinical or electrocardiographic evidence of myocardial infarction were not included in this series. Such isolated, small myocardial scars in the septum have been given special consideration previously[10] and will be discussed in further detail in a subsequent report.



FIGS. 1 and 2. (*See legend opposite page.*)

o generally accepted pathologic criteria exist fo left and right ventricular hypertrophy; those ba d on the tables of Saphir[11] were used in this st ly. These criteria are reliable when hypertr hy is pronounced and definite but not when it borderline. Errors may well exist, however, in isolated instances of early hypertrophy in a sm ll heart in which the muscle mass does not ex ed the upper limits of normal for the group.

eft ventricular hypertrophy (LVH) was consid red to exist if (1) thickness of the left ventri ular wall, excluding any trabeculation, exceeded 15 mm. at a site 1 cm. below the valvular rin near the septum anteriorly or if (2) the wei ht of a heart exceeded the expected mean for the height and weight of the subject by more than two standard deviations.[12] Such criteria as the appearance of a dilated chamber, hypertrophy of the trabeculae carneae, or a lower minimum of thickness of the left ventricular wall were rejected as equivocal.

Unfortunately, the criteria for right ventricular hypertrophy (RVH) were less definitive: (1) pronounced dilatation of the right ventricular chamber, (2) hypertrophy of the trabeculae carneae, or (3) thickness of the right ventricular wall, excluding any trabeculation, of 5 mm. or more at a site near the septum just below the region of the pulmonary conus. Thicknesses of 4 to 5 mm. were regarded as equivocal and were so recorded, and such specimens were not considered to exhibit right ventricular enlargement if criteria (1) and (2) were absent.

The generally accepted electrocardiographic criteria of myocardial infarction were used.[13-14] The spatial vectorcardiographic criteria of infare-

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FIG. 1 *Left.* Summary of the clinical, anatomic, electrocardiographic, and spatial vectorcardiographic data for 33 patients with posterior myocardial infarction. *The key to symbols is in figure 2.* The clinical features are listed in the following order: (*C*) cancer, (*F*) congestive failure, (*AP*) angina pectoris, (*I*) myocardial infarction, and (*E*) enlarged heart demonstrable roentgenographically. The presence of (*C*) or (*E*) is indicated by a solid block, their absence by a blank. The number of years of congestive or anginal failure is recorded under items (*F*) and (*AP*) except when noted only terminally (*T*), and the number of clinically recognized episodes of infarction under (*I*). In the second column, concerned with the coronary arteries (*Cor. A*), L_A indicates left anterior descending artery, L_C left circumflex artery, and R_P right posterior descending artery. *Solid block*, arterial occlusion; *N*, extreme narrowing; *blank space*, patency. In the third column, the position and depth of the predominant myocardial lesion are shown according to division of the myocardial wall into thirds: *N*, subendocardial; *M*, intramural; and *P*, subepicardial. In the fourth column the anatomic sites of lesions are indicated. The left ventricular cone was considered unrolled and projected on a rectangular grid divided into *S*, septal; *A*, anterior; *L*, lateral; and *P*, posterior or diaphragmatic quadrants according to conventional landmarks[16] and the anatomic localizations shown at the bottom of figure 2. Each quadrant was divided into thirds, i.e., basal, central, and apical sectors. The predominant lesion for each vertical half-sector was recorded. A similar notation was employed for localization of the lesion as suggested by the conventional electrocardiogram and spatial vectorcardiogram except that all were indicated arbitrarily on the central sector of the grid. However, the vectorcardiographic finding of terminal deformity is appropriately indicated in the grid for the posterolateral basal area. In the column for right and left ventricular hypertrophy, *A* indicates that the diagnosis was made on the basis of evidence obtained at necropsy, *E* on the basis of the electrocardiogram, and *V* on the basis of the vectorcardiogram. Ventricular weights were determined after trimming off the vessels and fat and, when measured after fixation, corrected to fresh weight by multiplying by the ratio of the fresh total weight of the heart to the fixed total weight of the heart.

FIG. 2 *Right.* Summary of the clinical, anatomic, electrocardiographic, and spatial vectorcardiographic data for 26 patients with anterior myocardial infarctions. *(See legend of figure 1 for key to abbreviations.)* In both charts, in the column labeled *Site*, the areas of transmural scar with pronounced thinning of the wall are the same as those of aneurysmal bulging except for patient no. 11 (anterior), in whom aneurysmal bulging was not accompanied by thinning. In the column indicating depth of involvement of the wall, the upper half of the block for patient no. 6 represents the predominant anatomic change in the septal wall and the lower half the predominant anatomic change for the anterior wall. Similarly, for patient no. 17, the upper half represents the basal aspect of the lesion and the lower half the apical aspect.

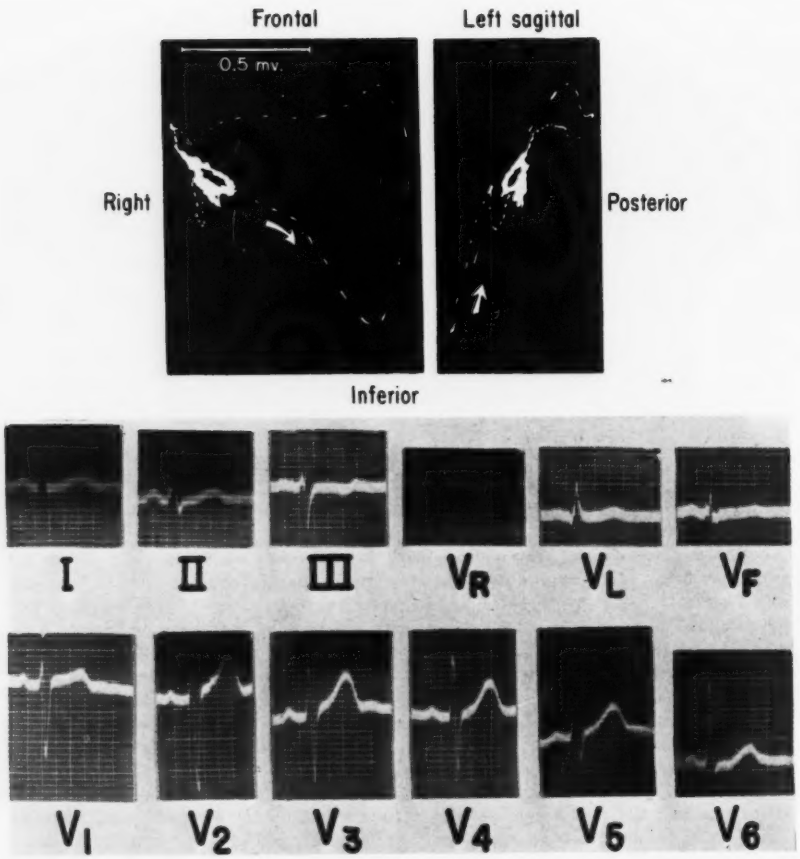

FIG. 3. *Top.* The spatial vectorcardiogram for a subject with a myocardial infarct of the diaphragmatic wall of the left ventricle (patient no. 4, fig. 1).

Bottom. The extremely early QRS sÊ-loop is not displaced upward (thus, no Q in lead III), but there is an early arc-deformity as a result of direction of the trace as though away from the infarcted zone.

tion used were those previously described,[7, 8] but the traces were carefully scrutinized in search of new criteria.

RESULTS

Results are summarized by figures 1 through 10 and tables 1 through 3. In general, the configurations of the ECG and sVCG varied according to previous expectations. Many of the hearts manifested multiple infarcts. Lesions were classified as *posterior* or *anterior,* depending on which predominated in size. Details of the anatomic location and description of the infarcts are presented in figures 1 and 2.

Posterior Infarcts

In posterior infarction the early portion of the QRS sÊ-loop of the sVCG was characteristically directed away from the centroid of the major infarct and toward the centroid of the heart. Thus, it was directed superiorly and to the left, frequently resulting in clockwise inscription in the frontal plane. Occasionally, with infarction of the diaphragmatic wall of the heart, there was upward arcing of the inferior edge of the QRS sÊ-loop involving the early, but not initial, portion of the loop (fig. 3). When the lateral wall was

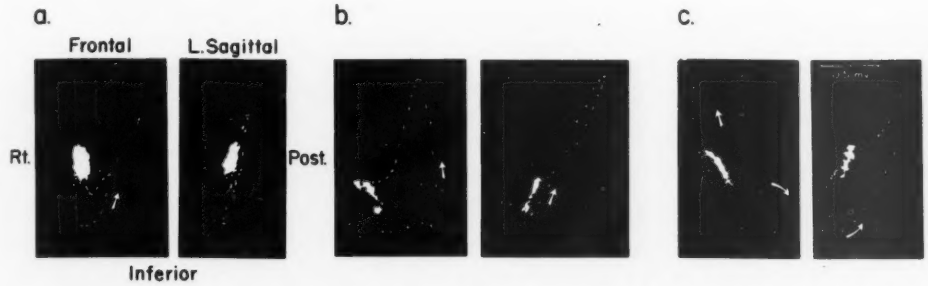

FIG. 4. Spatial vectorcardiograms of 3 subjects with posterior or lateral basal scarring showing variation in deformity of the late portions of the QRS sÊ-loop. The late peak in the QRS sÊ-loops, followed by the dip just before the isopotential point, is referred to in the text as the deformity of the terminal limb. These 3 sVCG also show associated alteration. For example, (*a*) (patient no. 16, fig. 2), the early posterior displacement of the QRS sÊ-loop reflects loss of electrically active muscle in the anteroseptal wall of the left ventricle. In (*b*) (patient no. 15, fig. 2), the early downwardly concave, arc-shaped deformity reflects loss in the diaphragmatic wall of the left ventricle and the rapid vertical upstroke reflects loss in the lateral wall of the left ventricle. In (*c*) (patient no. 11, fig. 1), both the upstroke of lateral loss and the characteristic deformity of the terminal limbs can be seen. Unlike the other 2 examples, the electrocardiogram of this patient did not fulfill the conventional criteria of myocardial infarction.

also infarcted, the midtemporal portion of the loop became straightened or arched, with the convexity directed to the right (fig. 4*b* and *c* and fig. 5*b* and *c*). When the infarct was "high," i.e., near the atrioventricular groove, and posterior or posterolateral, a characteristic deformity[7, 8] appeared in the terminal portion of the QRS sÊ-loop, consisting in extremely upward peaking of the trace, followed by a downward dip (or arc with upward concavity) (figs. 4 and 5). All these displacements of appropriate portions in time of the QRS sÊ-loop, which may be visualized as directed away from the infarcted zone, perhaps resulted from loss of electric activity that would have normally originated in the infarcted areas. This holds not only for the early portions of the QRS sÊ-loop but also for any other later portions, as has been discussed previously.[7, 8]

In 6 of the 33 hearts (18 per cent), posterior infarcts were found at necropsy when infarction had not been suspected from either the ECG or the sVCG. On careful re-examination of spatial vectorcardiographic traces of these hearts, after completion of the anatomic and pathologic studies, we still failed to find electrocardiographic or spatial vectorcardiographic evidence of infarction. Figure 1 shows the location of these "infarcts" in each heart. Evaluation of the pathologic diagnosis of these 6 hearts provided two interesting characteristics: 1. In 5 of these hearts, the "infarct" was composed not of a large single fibrotic scar but rather of many small, isolated, irregular scars of a few millimeters in diameter, which tended to coalesce. In all instances, however, myocardial tissue around and among the small scars appeared normal (fig. 6). 2. In 3 of the hearts, complete occlusion was not detectable in any coronary artery.

Thus, it appears that such a lesion is not an infarct in the usually accepted sense but is rather a multiplicity of small scars grouped together to give the impression, on casual inspection, of a large, single infarcted area or scar.

As shown in table 1, there was a preponderance of lesions of stippled or coalescing fibrosis among the hearts with posterior infarction. However, when all the examples of discontinuous fibrosis of both posterior and anterior classifications were grouped with all small in-

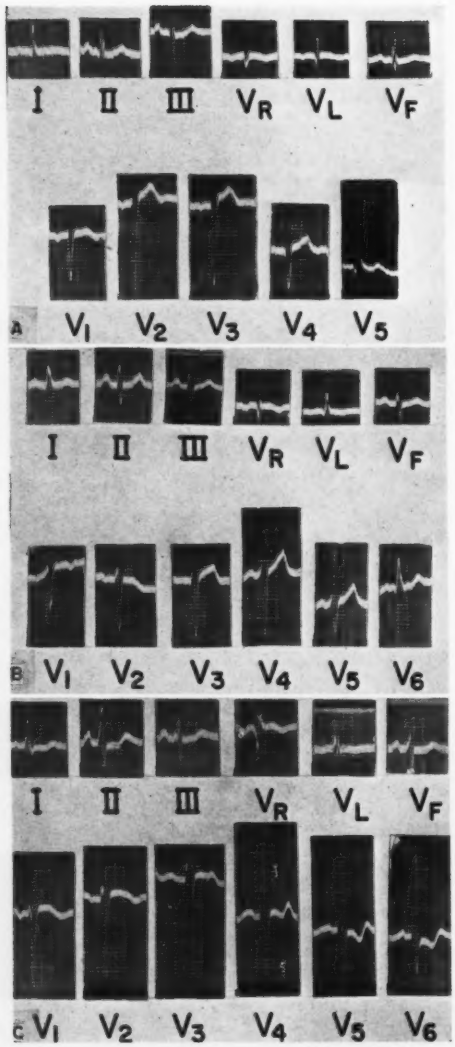

FIG. 5*A-C*. ECG's corresponding to 4*A-C*.

tramural scars and contrasted to the larger, solid, subendocardial or transmural infarcts and scars, certain relations appeared. Of 31 examples of the first group with "minor" infarction, 22 patients had died as a result of cancer and its complications or from unrelated diseases (ruptured peptic ulcer or fracture of the skull with bronchopneumonia). Thus, only 9 had symptomatic heart disease, and only 4 of these had had clinically recognized angina pectoris or episodes of myocardial infarction. In the second group with "major" infarctions, the clinical state and death of the patient were dominated by cancer in only 5 of 28 instances but by symptomatic heart disease in 23 instances, in 22 of which angina pectoris or clinically recognized episodes of myocardial infarction had been evident. The diagnosis of infarction, on the basis of the ECG and sVCG, was missed in the group with minor infarction on 9 occasions but in that with major infarction only once.

Accuracy of the diagnosis of posterior infarction from both ECG and sVCG is summarized in tables 1 through 3. An unequivocal diagnosis of posterior infarction was made from the ECG alone in 12 of the 33 cases (36 per cent) and from the sVCG alone in 8 cases (24 per cent). In 9 cases (27 per cent), strongly suggestive evidence was found in the sVCG alone and in 4 cases (12 per cent), in the ECG alone (table 3). Thus, the clinical and other data were of considerable importance in arriving at the correct diagnosis before death. From the sVCG of 6 of 21 patients, an accurate diagnosis of a high or basal posterolateral infarct was made on the basis of the terminal deformity in the QRS sÊ-loop. In 5 of these instances, this infarct was not suspected from the ECG, although late changes in the QRS complex were subsequently interpreted in other tracings, before death of the patients, as suggestive evidence of high or basal infarction.

The general location of the posterior infarcts for 33 hearts and the accuracy of electrocardiographic and spatial vectorcardiographic diagnoses are indicated in table 2. The sVCG and the conventionally recorded ECG were equally accurate in the diagnosis and localization of the posterior infarcts if the mid and late deformities of the QRS sÊ-loop were considered. The "arc-shaped" deformities in the midportions and the terminal deformities of the QRS sÊ-loops are new yet recognized criteria of infarction manifested by the spatial vectorcardiogram. The ECG undoubtedly displays associated deformities

TABLE 1.—*Infarctions Classified by Site and by Character*

Infarction	No. cases	Symptomatic heart disease	Apical lesion	Diagnosis missed by		
				ECG	aVCG	ECG & aVCG
Site						
Posterior	33	14	17	15*	12	6
Anterior	26	18	24	5	7	4
Character						
Spotty fibrosis and intramural scars	31	9	18	17*	15	9
Solid scars or infarcts	28†	23	23	3	4	1
Total	59	32	41	20*	19	10

*In the ECGs of 3 patients with scattered fibrosis of the posterior wall, the only sign of abnormality was absence of Q in I, V_5, and V_6. Thus, 3 fewer diagnoses than indicated were missed when this criterion was used.

†Includes arbitrarily one fresh intramural infarct (no. 4 of fig. 1) surrounded by transmural coalescent fibrosis.

at the same time in the cycle, but their recognition has simply not yet been developed. Studies of Langner[15] indicate the value of higher fidelity and more rapid paper and film speed in electrocardiography for demonstrating such changes, but recent experience suggests that some of them can be detected with conventional recording technics. However, whether or not this can be made clinically reliable without improvement in recording technic remains to be determined.

The presence of RVH and LVH did not seem to impair the accuracy of electrocardiographic more than vectorcardiagraphic inter-

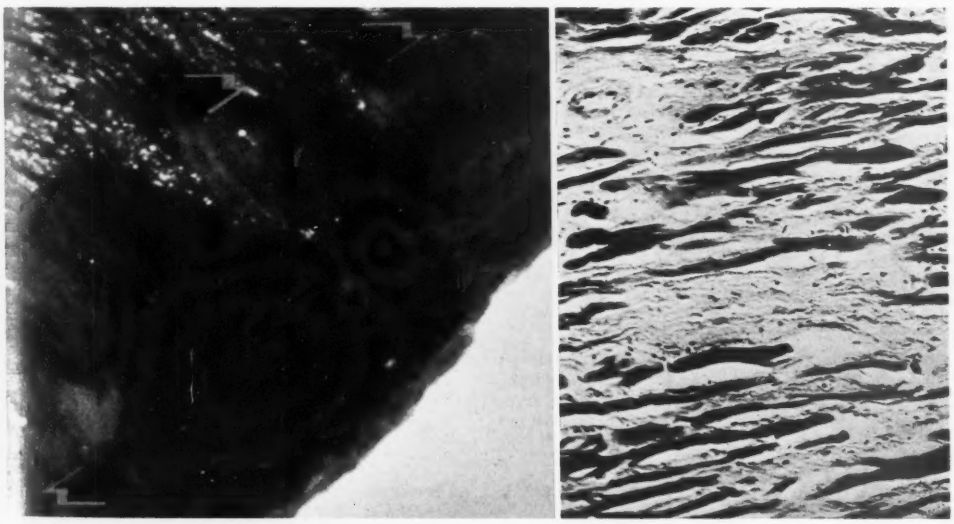

FIG. 6 *Left.* Cross section of the posteroseptal wall of the left ventricle of a heart with small areas of coalescing fibrosis. The fine stippling throughout the myocardium is visible in the photograph, with clusters of small scars indicated by the arrows; others can be seen on close inspection of the illustration. *Right.* Microscopic appearance of a section of the left ventricular wall of a heart with coalescent myocardial scarring. Note persistent muscle fibers coursing through the regions of scarring.

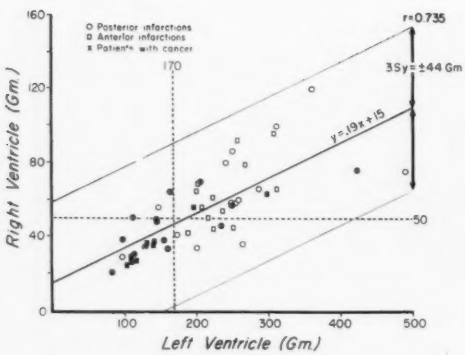

FIG. 7. Relation of the right and left ventricular masses of 50 of the hearts with myocardial infarction with symbols to indicate the site of infarction and the presence or absence of cancer. Maximal arbitrary normal limit was set at 50 Gm. for right and 170 Gm. for left ventricular weight. The estimate of hypertrophy by thickness of the wall is not shown but corresponded well to the weight.

pretation of the infarction. Interestingly, either RVH or LVH was considered to be present, on the basis of the ECG and sVCG, on 4 occasions when it did not actually exist. This type of error is known to occur in myocardial infarction, but the mechanisms and reasons therefore are not clear.

The relation of the size of ventricles to each other and to infarction is shown in figure 7. The 2 ventricles were directly related to each other in size regardless of total weight. Posterior and anterior infarctions were about equally frequent in the normal sized hearts and in those with hypertrophied ventricles (fig. 7). The ventricles of patients with malignant disease were usually small, even in the presence of infarction.

Anterior Infarcts

The spatial vectorcardiographic changes diagnostic to anterior myocardial infarction were essentially as previously described[1–12] an abnormal early part of the QRS sÊ-loop directed as though away from the infarcted zone toward the centroid of the heart (fig. 8).

The postmortem studies suggested some points of interest that deserve special comment. In 7 of the 26 hearts (27 per cent) in

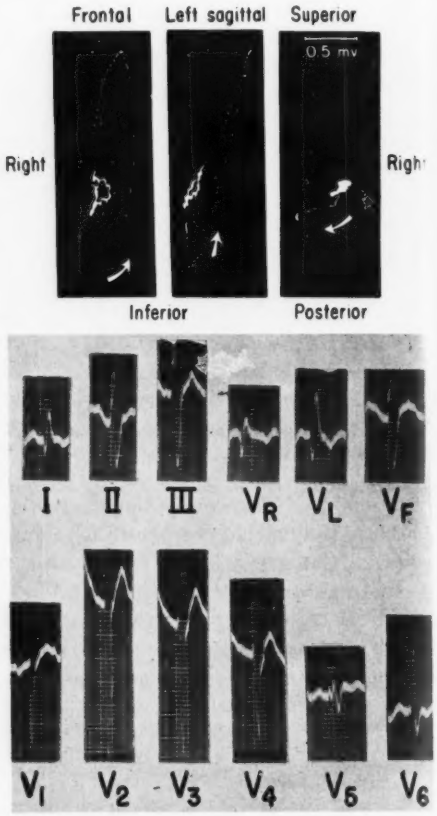

FIG. 8. Spatial vectorcardiogram of a subject with anteroseptal myocardial infarction (patient no. 6, fig. 2). Note that in the superior planar view the direction of inscription of the early portion of the QRS sÊ-loop is to the right and then posteriorly, thus in a clockwise direction away from the anteroseptal junction rather than in the normal counterclockwise direction.[10]

which anterior myocardial infarcts were found at necropsy, the infarction was not detected from the sVCG (table 1). Four of these, however, were instances of multiple small scars with intervening areas of nonscarred tissue; they presented precisely the same problem described for the multiple coalescing scars in posterior infarction. One heart had a small subendocardial scar beneath apparently viable muscle. Classical left bundle-branch block in one of the patients

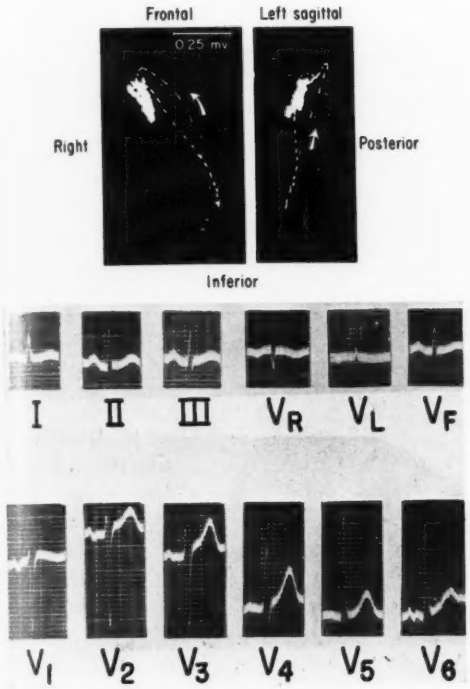

FIG. 9. Spatial vectorcardiogram of a subject with septal basal coalescing scars (patient no. 3, fig. 2), in whom infarction was not clearly detected from the ECG or sVCG. The diminished Q in leads I, V_5, and V_6 suggested the possibility of septal fibrosis.

prevented detection of infarction by either sVCG or ECG. For reasons to be discussed, not all such lesions need be expected to produce vectorcardiographic or electrocardiographic abnormalities of sufficient degree to lead to an interpretation of infarction (fig. 9). However, subtle changes of diagnostic importance may exist in these traces, awaiting recognition, since the ECG taken several weeks later was considered to reflect infarction or fibrosis in 2 of the 7 hearts (patient nos. 2 and 26, fig. 2). This may represent a change in conduction about the area of fibrosis, for the pathologic appearance was that of scarring and fibrosis of long standing in each instance. The general location of all the anterior infarcts is shown by table 2.

The accuracy of electrical diagnosis of anterior infarction is summarized in table 3. Accuracy of recognition of the anterior infarcts by sVCG or ECG did not generally differ, except in an occasional patient.

The terminal deformity in the sVCG, although of supplemental use in this group, did not enhance detection of basal scarring and infarction overlooked on ECG, in contrast to the experience with posterior infarctions (figs. 1 and 2). In only one patient with anterior infarction was the terminal deformity in the sVCG the sole diagnostic sign. This may be explained on the basis of the more extensive nature of the infarctions in this group of patients. Also noteworthy is the fact that the terminal deformity appeared in

TABLE 2.—*Infarctions not Diagnosed Electrically by Site of Lesion*

Site of lesion	No. infarctions	Diagnosis missed by ECG	sVCG	ECG & sVCG
Posterior				
Strictly posterior	5	4	1	1
Strictly lateral	4	2	3	2
Lateral and slightly anterior	2	1	1	1
Posterolateral	6	3	1	1
Posterolateral and slightly anterior	6	1	1	0
Posterolateral and septal	10	1	5	1
Subtotal	33	12*	12	6
Anterior				
Strictly septal	4	2	2	1
Predominantly anterior	5	2	3	2
Apical and posteroseptal	4	1	1	1
Widespread	13	0	1	0
Subtotal	26	5	7†	4
Total	59	17*	19	10

*This sum excludes 3 instances in which the only electrocardiographic evidence of abnormality was absence of Q in I, V_5, and V_6; lesions of the posterior wall but not septal wall were found at necropsy. Thus, if included, these tracings would increase total numbers of those missed to 15 and 20, respectively.

†This sum includes 2 instances in which the lesion was missed in sVCG but suggested in ECG several weeks later, after clinical evidence of a new, fresh infarct had appeared.

TABLE 3.—*Accuracy of Electric Diagnosis of Infarction*

Evidence of infarction	Electrical diagnosis: Posterior Infarct ECG	Posterior Infarct sVCG	Anterior Infarct ECG	Anterior Infarct sVCG
Unequivocal by conventional criteria	12	8	17*	12
Strongly suggestive	4	9	1*	6
Suggested by terminal deformity only (sVCG)		4		1
Suggested by absence of Q in I, V_5, and V_6 only (ECG)	5		3†	
Total accurate	21 (63%)	21 (63%)	21 (81%)	19 (73%)
Missed	12	12	5	7
Grand total	33	33	26	26

*Six examples of pseudoblock pattern included.

†Septal lesions found at autopsy.

3 cases of anterior infarction with posterolateral involvement *without*, as well as in 5 cases *with* basal involvement.

The general anatomic location of the infarcts in the 26 hearts in which anterior infarctions predominated is shown in table 1 and figure 2. Nineteen of the 26 hearts had lesions of the posterior wall as well, however. It has long been known that the presence of a posterior lesion may render vectorcardiographic or electrocardiographic detection of anterior infarction more difficult.

As with the varieties of posterior infarction, the loss of electric activity in the region of infarction reduced the local contribution to the successive mean instantaneous vectors. Thus, appropriate portions of the QRS sÊ-loop were, in general, displaced or oriented away from the region of infarction toward the centroid of the heart.

Posterior and Anterior Infarction

The over-all differences in clinical, pathologic, and electric manifestations of the "posterior" and the "anterior" infarcts are presented in figures 1 and 2. As previously noted, anterior infarction was found primarily in patients with symptomatic heart disease and posterior infarction in patients with clinically concealed or asymptomatic heart disease. The anterior descending branch of the left conorary artery was grossly narrow or occluded in all except 2 of 25 instances of anterior infarction in which the coronary arteries were specifically examined; in both of these, however, the apical myocardium was involved, with subsequent electric detection. In only 16 of 31 instances of posterior infarction was the anterior descending branch of the left coronary artery grossly narrow or occluded. In 9 of the remaining 15 the apical myocardium was not involved, and in 6 of these the infarct was not detected from the ECG.

In 3 of these 6, the infarction was detected solely from the sVCG, by its terminal deformity, whereas in the other 3 it was completely missed. The apical portion of the myocardium was involved in all except 2 of the 26 hearts with anterior infarcts but in only 17 of the 33 with posterior infarcts. With allowance for differences in sampling, there is, thus, a rought clinical and anatomic similarity between the group with posterior infarcts and group I of Sayen, Sheldon, and Wolferth[16] and between our group with anterior infarcts and their groups II through IV.

Left and Right Ventricular Hypertrophy

The left ventricle was hypertrophied in 20 of the 26 hearts with anterior infarction. Thirteen of these hearts had right ventricular hypertrophy also, and another had right ventricular dilatation (fig. 2). Right ventricular hypertrophy was detected from the ECG in 3 instances and from the sVCG in none, whereas left ventricular hypertrophy was detected from the ECG in 10 instances (3 only suggestive) and from the sVCG in 15. The

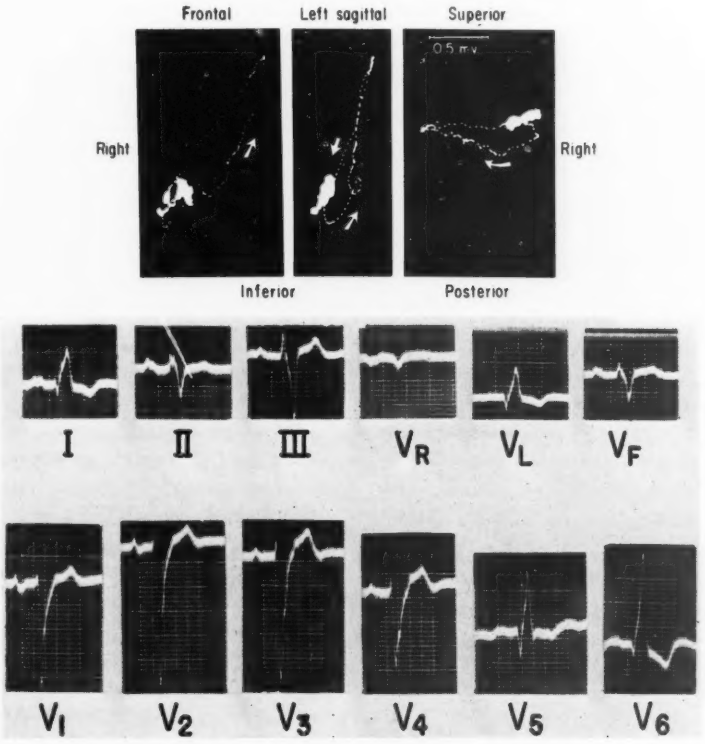

FIG. 10. Spatial vectorcardiogram and electrocardiogram of a subject with anteroseptal and postero-apical myocardial infarction with aneurysmal bulging of the thinned scar in the central portion of the septum (patient no. 22, fig. 2). The superior planar view shows the abnormal rightward and clockwise inscription, which is associated with the early, abnormal, downward deflection in lead I. This configuration of the QRS s£-loop is probably partly due to the left ventricular hypertrophy.

accuracy of diagnosis was increased slightly when both types of recordings were used together.

The anterior infarct was missed electrocardiographically in 1 of the hearts with left or right ventricular hypertrophy or both. One heart also had a left bundle-branch block, which is expected to reduce the diagnostic reliability of the ECG, although it has not yet been proved to be a complete handicap in interpreting the sVCG.

In general, ventricular hypertrophy presented essentially similar problems for detection of anterior infarction from the ECG and sVCG as discussed previously for posterior infarction. In only one patient with anterior myocardial infarction did both the ECG and sVCG suggest the presence of hypertrophy when it did not exist. This may be attributable to the localization and extent of the infarcts in this heart.

Ventricular Aneurysms

There were 11 ventricular aneurysms, 3 of which were in a miscellaneous group composed of a posterolateral, a posteroseptal, and an apical and posteroseptal infarct. Infarction in the other 8 instances involved either 3 or 4 of the "quadrants" of the left ventricular cone. Six of these 8 patients with aneurysms associated with extensive myocardial infarction exhibited a common electro-

cardiographic pattern: an abnormally prolonged and predominantly upright QRS with a wide, early downward deflection, due to infarction, in leads I, V_L, V_5, or V_6 or any combination of these. The corresponding QRS sÊ-loop was relatively long, narrow, pointed, and directed upward, slightly to the left, and posteriorly (fig. 10). The trace was inscribed slowly and slightly irregularly, the early portion being to the right of, and posterior to, the isoelectric point. All the loops considered typical had small concave arcs directed downward in some portion of the QRS sÊ-loop, suggesting infarction of the diaphragmatic myocardial wall, in addition to the early "anterolateral" arc deformity seen best in the superior plane.

Discussion

These studies reveal certain interesting points. For example, instead of a single large scar, 31 hearts had many small, separate, coalescing scars with microscopic evidence of apparently normal muscle distributed among the fibrotic areas. The muscle could have been active enough electrically to produce complexes that did not exhibit evidence of infarction in the ECG and sVCG. Perhaps the plan of choosing subjects who were expected to die soon had the effect of emphasizing 2 bands in the spectrum of myocardial infarction-coronary artery disease. Two disease groups provided most of the material for study: (1) patients who were dying from cancer but whose health had never been seriously jeopardized by their myocardial damage and (2) patients who were dying from serious, symptomatic heart disease produced by repeated major infarction and scarring.

These observations are of interest, first, because a better understanding is needed of the term "infarction" as interpreted by the clinician and pathologist and, second, because absence of electrocardiographic and spatial vectorcardiographic findings suggestive of infarction in a heart with apparent postmortem evidence of an infarct requires better understanding.

Possibly the subjects with lesser degrees of infarction may have had repeated episodes of angiospasm, with or without pain, and, perhaps, occlusion of small vessels with resultant death of small segments of myocardium with formation of a scar. Conceivably, small segments of muscle may also have been injured during the periods of coronary insufficiency, with only gradual death of the segment and formation of scar; several episodes of insufficiency of coronary blood flow and associated disturbances may have been required before death of the segment occurred. In any event, the mechanism by which the scars formed is unknown, but the resultant lesions or "tombstones" were evident at necropsy. Fibers of electrically active myocardium probably coursed around and among the myriad scars. With depolarization and repolarization of these fibers, as much as 90 mv. of potential difference could have been produced across the cellular wall, so that sufficient electric sources among these coalescing scars remained to maintain an essentially adequate order of electric activity throughout the cardiac cycle. Some alterations must have been produced, but they were minor and too subtle to be detected in the records. Septal scars and fibrosis have been shown to produce alterations in the Q wave in certain leads of the ECG of some subjects.[9] This type of anatomic or structural alteration is not merely of academic interest but is of considerable practical importance, especially if the ECG and sVCG are to be evaluated properly from both experimental and clinical points of view.

It would appear preferable, therefore, to regard the lesions in the first group as multiple, coalescing, small scars rather than as a single large infarct. The clinician and pathologist may interpret these lesions as each wishes, but any confusion resulting from arbitrary inclusion of both kinds of lesions in a single diagnostic category of infarction is to be avoided if proper electrocardiographic and vectorcardiographic criteria of diagnosis are to be established. Not only are these lesions anatomically and electrocardiographically different but they may also differ in other respects.

More careful postmortem inspection of the heart for disease is seriously needed. All too frequently, the postmortem report supported by a cursory pathologic examination is erroneously considered the final verdict. Only if the postmortem study is adequate should it be considered indisputable. It is believed that slicing of the unrolled left ventricular cone parallel to the endocardial and epicardial surfaces will display the extent of gross myocardial lesions to best advantage. Multiple serial layers may thus be inspected by means of serial slicing. Conventional ring slices fail to reveal adequately, if at all, some of the small lesions, but preference of technic is an individual matter. The significant requirement is a careful, thorough study to insure reliable information. The type, size, location of lesions and associated observations should be carefully described in detail to permit critical clinical, electric, and anatomic correlations.

The temporal phases of electrocardiographic and vectorcardiographic phenomena should also be considered more carefully. Changes in the ECG and sVCG can reasonably be expected to occur during the intervals appropriate for activation of the diseased segment of the myocardium. The present studies confirm the previously introduced impressions[7, 8, 17] that detectable changes in the later portions of the QRS sÊ-loop occur when infarction exists in those portions of the myocardium that are depolarized later in the accession process. Although these sVCG changes are readily recognizable, it was not always possible to see such alterations in the ECG. Thus, attention must be directed beyond the early portions of the ECG and sVCG for detection of infarcts in all portions of the myocardium. During interpretation, the complexes of the ECG and sVCG must be considered temporally, not only from one cardiac cycle to the next but also within each cycle in relation to the simultaneously occurring electric and other physiologic phenomena of all portions of the myocardium.

The diagnosis of ventricular enlargement and hypertrophy by either ECG or sVCG was poor. The high incidence of combined hypertrophy, with the electric effects of one enlarged chamber tending to neutralize that of the other, may account for this. The criticism of den Boer[18] should be kept in mind when attempts are being made to distinguish left ventricular hypertrophy from anterior myocardial infarction; similar orientation of the QRS sÊ-loop may result from either. However, in some instances of posterior myocardial infarction, the classical pattern of LVH was deformed only by an otherwise paradoxic upward displacement of the early portions of the QRS sÊ-loop. Left ventricular hypertrophy was not suspected from the electrocardiogram, but both lesions were readily suspected from the sVCG.

Experience is necessary to detect readily deformities that indicate specific lesions in the heart. Spatial vectorcardiograms recorded by other methods and reference systems should display changes essentially analogous to those described in this report, provided the methods and reference systems conform to certain general requirements for satisfactory recording of the sVCG.[19] Of course, direct observations with postmortem correlations are necessary to evaluate the accuracy of this statement. Similarly, further inquiry should be made into the repolarization process,[20] which may be as revealing as closer scrutiny of the depolarization complex has been. Although the TsÊ-loops and T waves were not studied extensively in these observations, they did not seem to depart from the patterns predicted by present-day concepts in vectorcardiography and electrocardiography.

The combination of clinical data and electrocardiographic and spatial vectorcardiographic findings resulted in a correct diagnosis of infarction before death in all but 5 instances. Failure to recognize in the ECG and sVCG evidence of infarction in about 15 per cent of the hearts that exhibited postmortem evidence of lesions is not surprising for general hospital medical and surgical services. The percentage would probably be smaller in a cardiologic service, with more careful and complete electrocardiographic exploration. Patients without definite electrocardiographic evidence of myocardial in-

farction are frequently, and appropriately, treated by the clinician for infarction, but with a certain element of doubt. This mental reservation on the part of the clinician sometimes arises from injudicious or excessive faith in the infallibility of interpretation of the tracings. The importance of reliable, meticulously obtained clinical information cannot be overemphasized in the diagnosis and proper management of infarction.

This study was undertaken not to determine whether the ECG or the sVCG was superior but rather to learn what may be obtained from the sVCG, to search for new vectorcardiographic indications of abnormality, and to investigate opinions previously expressed concerning the sVCG and ECG. Our observations indicate the necessity for evaluating the interpretation of the ECG and the sVCG at necropsy. A few fibers of viable and electrically active muscle dispersed among the scars (fig. 6) would probably be sufficient to minimize the traditionally recognized diagnostic electrocardiographic alterations of myocardial infarction. The discrepancy between electric and pathologic diagnoses emphasized the need for studying in greater detail the configurations of the ECG and sVCG in search of reliable, but presently unrecognized, alterations diagnostic of infarction, however subtle they may be.

Summary and Conclusions

Of 160 unselected consecutive necropsies of patients in whom the electrocardiogram and spatial vectorcardiogram were recorded shortly before death, 59 hearts had myocardial infarcts. The ECG and sVCG were carefully analyzed with respect to postmortem findings in the heart. Thirty-three myocardial infarcts were classified as predominantly posterior and 26 as predominantly anterior. Right ventricular enlargement was recorded in 26 instances, left ventricular enlargement in 37, combined ventricular enlargement in 24, and ventricular aneurysms in 11.

In addition to previously described total and segmental displacements of the QRS sÊ-loop with resultant arcs, abrupt shortening, and other deformities of the QRS sÊ-loop characteristically directed as though away from the infarction, a deformity of the terminal limb was observed for high or basal posterolateral infarction. This deformity consisted of pronounced upward peaking, followed by a downward dip or arc with upward concavity. The interpretations of the sVCG and ECG were equally efficient in the detection of anterior and posterior infarction, there being individual differences among patients.

Of the 11 patients with ventricular aneurysms, 6 had a similar electrocardiographic pattern: predominantly upright, abnormally prolonged $\bar{Q}RS$ with a definite, early, downward deflection in leads I, V_L, V_5, or V_6, or any combination of these. This was different from that of either LBBB with septal infarction or lateral infarction with a prolonged QRS complex. The QRS sÊ-loops of 7 patients were alike; they were directed primarily upward and slightly to the left and posteriorly, with early displacement to the right of, and posterior to, the isopotential point and with arching deformities suggestive of both anterolateral and posterior myocardial infarction.

Perhaps related to the high incidence of combined ventricular hypertrophy was a low incidence of electrocardiographic or vectorcardiographic diagnosis of ventricular hypertrophy. Additional interference with the diagnosis of infarction may have resulted, but there was a fairly consistent direct relation between the sizes of the right and left ventricles regardless of total weight of the heart. The T sÊ-loops seemed to obey previous predictions for alterations produced by infarction.

Further physiologic, as well as more detailed anatomic, study will be necessary to evaluate more thoroughly the relation between the electric events of the heart and the clinical and pathologic state of the myocardium.

Summario in Interlingua

In un serie de 160 non-seligite necropsias consecutive de patientes pro qui electrocardiogrammas e spatio-vectocardiogrammas

haveva essite registrate brevemente ante morte, infarctos myocardial esseva incontrate 59 vices. Le electrocardiogrammas e le spatio-vectocardiogrammas esseva analysate deliatemente con respecto al constatationes facte in le cordes post morte. Trenta-tres infarctos myocardial esseva classificate como predominantemente posterior e 26 como predominantemente anterior. Allargamento dextero-ventricular esseva registrate in 26 casos, allargamente sinistro-ventricular in 37 casos, combinate allargamento ventricular in 24 casos, e aneurysmas ventricular in 11 casos.

A parte le previemente describite displaciamentos total e segmental del ansa sÊ de QRS con resultante arcos, accurtation abrupte, e altere deformitates del ansa sÊ le quales es characteristicamente orientate de maniera a suggerer le tendentia a distantiar se ab le infarcimento, un deformitate del segmento terminal esseva observate pro infarcimentos posterolateral alte o basal. Iste deformitate consisteva de un pronunciate dentiformation in alto, sequite per un valle o un arco a concavitate in alto. Le interpretationes del electrocardiogrammas e del spatio-vectocardiogrammas esseva equalmente efficace in le detection de infarcimento anterior e de infarcimento posterior, con differentias inter le patientes individual.

Ex le 11 patientes con aneurysma ventricular, 6 habeva simile configurationes electrocardiographic: Un predominantemente erecte e anormalmente prolongate QRS con un definite precoce deflexion in basso in le derivationes I, V_L, V_5, o V_6 o un combination de istos. Iste configuration differeva ab illo de bloco de branca sinistre con infarcimento septal o infarcimento lateral con prolongation del complexo QRS. Le ansas sÊ de QRS de 7 patientes esseva le mesmes. Illos habeva un direction primarimente in alto e levemente postero-sinistrorse, con displaciamento precoce al latere dextere, posterior al puncto isopotential e con deformitates arcante que suggere infarcimento myocardial tanto anterolateral e etiam posterior.

Possibilemente relationate con le alte incidentia de combinate hypertrophia ventricular esseva un basse incidentia de diagnoses electrocardiographic o vectocardiographic de hypertrophia ventricular. Il es possibile que un interferentia additional con le diagnose de infarcimento esseva le resultato, sed il existeva un satis constante relation inter le dimensiones del ventriculos dextere e sinistre, sin reguardo al peso total del corde. Il pareva que le ansa sÊ obediva previe predictiones in re le alterationes producite per infarcimento.

Studios physiologic additional e etiam plus detaliate studios anatomic va esser necessari pro evalutar plus precisemente le relation inter le evenimentos electric del corde e le stato clinic e pathologic del myocardio.

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Evans, W., and Pillay, R. K.: Additional Electrocardiographic Signs of Cardiac Pain. Brit. Heart J. **19**: 366 (July), 1957.

The authors analyzed 1950 electrocardiograms to determine the significance of depression of the T-U segment and of the presence of natural Q waves in certain leads. A trough-like deformity of the T-U segment extending below the level of the U-P segment was not found in 500 electrocardiograms of healthy adults. It was observed once (Fallot's tetralogy) in 250 patients with noncoronary heart disease and among 15 with cardiac pain it was the only abnormality in 7. A natural Q wave in adults is defined as one not over 0.04 second wide and between 1 to 3 mm. deep except in lead 3 where it may be deeper. Among 500 electrocardiograms in healthy adults natural Q waves were not isolated to leads 1, 2, 3 or CR_4 or confined to the following combinations of leads: 1 and 2; 1 and CR_4; 2 and CR_4; CR_4 and CR_7; 1, 3 and 3R; 1, 2 and CR_4; 2, CR_4 and CR_7; 1, 3, 3R and CR_7; 2, 3, 3R and CR_4; 3, 3R, CR_4 and CR_7; 1, 2, 3, 3R and CR_4; 1, 3, 3R, CR_4 and CR_7. For this reason, natural Q waves so occurring were regarded as evidence of myocardial injury. Although natural Q waves in leads 1, CR_4 and CR_7 are found in healthy adults, the combination occurred so much more frequently in older persons and those who later developed myocardial infarction that this combination may likewise prove to be an early electrocardiographic sign of a myocardial injury.

SOLOFF

Serum Phospholipids

Genetic and Environmental Influences

By Louis E. Schaefer, M.D., David Adlersberg, M.D., and Arthur G. Steinberg, Ph.D.

Serum phospholipid levels were determined in 1,067 healthy persons aged 2 to 77 years. Phospholipid levels increased with age but in a different way for each of the sexes. The age-sex changes of serum phospholipids were similar to those observed for serum cholesterol. Correlation coefficients in members of 156 families indicated that the genetic factor is of importance in determining the serum phospholipid level in health. Because of the age-sex variations of serum phospholipid and serum cholesterol levels, no single arbitrary line can be drawn between normal and abnormally elevated levels of these 2 serum lipid fractions.

THERE is increasing evidence that atherosclerosis is a problem with many facets. Extensive investigative work is being conducted on the role of abnormal lipid metabolism as well as carbohydrate and protein metabolism in atherosclerosis. Factors such as thrombogenesis, blood coagulation, fibrinolysis, arterial wall injury, intimal hemorrhage, and others are also subjects of intensive study.[1, 2]

Most investigators, however, are mainly concerned with the part played by lipids in the genesis of atherosclerosis. At one time these studies centered around serum cholesterol and cholesterol metabolism. In recent years the interest in this field has been focused on aspects of lipids and lipoproteins other than cholesterol. For example, it is believed by some that the concentration of triglycerides in the serum may be an important factor in atherogenesis.[3] It has been shown in animals that increase in serum triglycerides results in a rise elevation of serum cholesterol and phospholipid.[4] Neutral fat transport and metabolism may thus be important in atherogenesis. The role of the nonesterified fatty acids in lipid transport and their possible relationship to carbohydrate metabolism have been investigated.[5, 6] In the study of dietary factors related to atherogenesis, the effect of saturated versus unsaturated fats is being carefully watched.[7]

In this connection the role of serum phospholipid deserves consideration. Its presence in atheromatous plaques and its synthesis in the arterial wall are well established.[8] Elevations or depressions of serum cholesterol are usually associated with changes in a similar direction of levels of serum phospholipid.[9, 10]

In contrast to extensive studies on serum cholesterol in relation to age, sex, endocrine factors, and such environmental factors as dietary, climatic, and occupational influences, relatively little information is available concerning corresponding changes of serum phospholipid. A detailed discussion of our present knowledge will be presented later.

It seemed profitable, therefore, to investigate systematically the levels of serum phospholipid in a normal population sample. The twofold purpose of the study was to establish possible relationships between age, sex, and serum phospholipid level, and to assess the relative importance of genetic versus environmental influences determining serum phospholipid levels in a healthy population.

Materials and Methods

The sample included 1,067 normal persons, 516 men and 551 women, aged 2 to 77. Among these were 156 families, consisting of 156 fathers, 156 mothers, and 268 children of these parents.

The 1,067 persons studied were part of the total sample of 1,236 persons of a healthy and unselected group of New York City employees

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TABLE 1.—*Ethnic Origin, Race, and Religion of Population Studied*

Population	Per cent
Ethnic Origin	
Italy	38
Ireland	25
England, Scotland	17
Germany	6
Scandinavian countries	3
Poland	3
France	3
Spain	2
Hungary	2
All others	1
Race	
White	98
Nonwhite	2
Religion	
Catholic	71
Protestant	20
Jewish	9
Moslem	<1

living in Staten Island, New York, who were investigated for the incidence and mode of transmission of idiopathic hypercholesterémia.[11, 12] A history was taken and a physical examination was performed on each person. The serums were analyzed for phospholipid by the Sperry modification of the Fiske-SubbaRow method and for total and esterified cholesterol by the Sperry-Schoenheimer method.[13, 14]

Ethnic origins, race, and religion of the persons studied are reproduced here from a previous publication[11] for the sake of completeness (table 1).

The overwhelming majority of these persons consumed a mixed American diet of the usual protein, carbohydrate, and fat content, similar in its composition to that described by Epstein et al.[15] for the working population in New York City.

SERUM PHOSPHOLIPID LEVELS

Analysis of the data shows that serum phospholipid level varies with age in a manner similar to serum cholesterol.[11] In males, the serum phospholipid level remains essentially constant through age 20 years, it rises sharply for the next 12 years (to age 32), and then it remains essentially constant until age 60 years (table 2). In females the serum phospholipid level remains constant until age 32 years and then rises gradually for the next 28 years until age 60. Our data are not extensive enough in the older age groups to determine the trend after age 60. As in the case of serum cholesterol, both males and females exhibit an increase in serum phospholipid levels with increasing age, and, again, as in the case of cholesterol, the increase starts earlier, lasts for a shorter time, and is more rapid in males than in females. The ultimate level in females, however, is greater than that in males (table 3).

TABLE 2.—*Changes in Serum Phospholipid Lev with Age in Males and Females*

Age interval (yr.)	No.	b*	p†
Males			
2-20	158	—1.323	.05
20-32	60	5.010	.001
32-60	298	0.338	.10
Females			
2-32	264	—0.296	.10
32-60	287	2.137	.001

*The average annual change of serum phosph lipid level in mg./100 ml. is represented by th coefficient b in the regression equation $Y = a + b$ where X = age in years and Y = serum phosph lipid level.

†Probability that observed value of b is an esti mate of an annual change which is zero.

The mean and upper 5 per cent levels of serum phospholipids for males age 2 through 20, and 32 through 60, and for females 32 through 60, were computed from the basic data. The appropriate regression equations were used to compute predicted values and upper 5 per cent levels for males age 20 through 32 ($y = 133.466 + 5.010X$) and for females aged 2 through 32 years ($y = 182.258 + 2.138X$).

The results of these calculations are presented in table 3. The upper 5 per cent levels listed in table 3 were used as age-and-sex specific standards for determining the presence of hyperphospholipemia.

Data are available for 156 families composed of mother, father, and at least 1 child, ("complete" families) and for another families in which serum phospholipids were determined for the father and at least 1 child, but not for the mother, and for 23 families

TABLE 3.—*The Mean or Predicted Level and Upper Five Per cent Values of Serum Phospholipids*

Age	Mean	Upper 5% Level	Age	Mean	Upper 5% Level
Males					
2-20*	227.2	295.3	27	268.7	335.5
20†	233.7	300.4	28	273.7	340.5
21	238.7	305.4	29	278.8	345.5
22	243.7	310.4	30	283.8	350.5
23	248.7	315.5	31	288.8	355.5
24	253.7	320.5	32	293.8	360.5
25	258.7	325.5	32—	282.5	364.2
26	263.7	330.5	60‡		
Females					
2-32§	243.1	312.7	46	280.6	362.8
32¶	250.7	332.9	47	282.7	364.9
33	252.8	335.0	48	284.9	367.1
34	254.9	337.2	49	287.0	369.2
35	257.1	339.3	50	289.1	371.4
36	259.2	341.5	51	291.3	373.5
37	261.4	343.6	52	293.4	375.7
38	263.5	345.7	53	295.6	377.8
39	265.6	347.9	54	297.7	379.9
40	267.8	350.0	55	299.8	382.1
41	269.9	352.1	56	302.0	384.2
42	272.0	354.3	57	304.1	386.3
43	274.2	356.4	58	306.2	388.5
44	276.3	358.6	59	308.4	390.6
45	278.4	360.7	60	310.5	392.8

*Based on 158 males between ages 2 and 20 years ($r = 41.4$).

†Means for ages 20 to 32 predicted from regression equation in table 2.

‡Based on 298 males aged 32 through 60 years inclusive ($r = 49.6$).

§Based on 264 females aged 2 to 32 inclusive ($r = 42.3$).

¶Means for ages 32 to 60 inclusive based on regression equation in table 2.

which serum phospholipids were determined for the mother and at least 1 child, but not for the father ("incomplete" families).

There were 5 "complete" families in which the father was hyperphospholipemic, and 5 in which the mother was hyperphospholipemic. Two (13 per cent) of the 15 children in these families were also hyperphospholipemic. There were 253 children in the remaining 146 "complete" families in which neither parent was hyperphospholipemic. Ten (4 per cent) of these children, 1 in each of 10 different families, were hyperphospholipemic. The difference between the frequency of hyperphospholipemia among the children of these 2 sets of families is not significant: it is, however, in the direction one would expect if there were a genetic component in the determination of hyperphospholipemia.

TABLE 4.—*Correlation Coefficients* between the Serum Phospholipid Levels of the Indicated Pairs*

	N	r	p
Mother-father	156	—.0147	$>.80$
Father-child	287	.2055	$<.001$
Mother-child	309	.2089	$<.001$
Sibling-sibling†	100	.2232	$.02<p<.03$
Father-son	139	.1785	$.03<p<.04$
Father-daughter	148	.2355	$<.01$
Mother-son	152	.3118	$<.001$
Mother-daughter	157	.1024	$\sim.20$

*All phospholipid levels were converted to equivalent levels for males aged 20 (as determined by the regression equation) to eliminate factors of age and sex.

†Intraclass r based on first and second siblings only.

Correlation analyses similar to those undertaken for the cholesterol levels[12] were computed for the phospholipid levels to check further on a possible genetic component. The correlation coefficients are shown in table 4.

The correlation between the serum phospholipid levels of mothers and fathers is essentially zero while that between fathers and their children, mothers and their children, and between siblings are each significantly different from zero and very similar to each other (upper part of table 4). There is no suggestion in these data, as there was in the data for serum cholesterol, that the correlation coefficient between father and child is lower than that between mother and child. Nevertheless, for completeness we have computed the correlation coefficients between father and son, father and daughter, mother and son, and mother and daughter. These correlation coefficients will be found in the lower portion of table 4. The presence of an important sex-linked genetic component in the determination of a character would lead to a relatively low correlation between father and son, a higher correlation between father

TABLE 5.—*Relation between Serum Levels of Cholesterol and Phospholipid*

	N	Regression of phospholipid (Y) on cholesterol (X)	Correlation between phospholipid and cholesterol
Males*	499	.715 ± .031	.715
Females†	510	.676 ± .027	.744

*Y_M 108.286 + 0.715X.
†Y_F 115.856 + 0.676X.

and daughter, which would be essentially equal to that between mother and daughter, and a still higher correlation between mother and son. The data in the lower portion of table 4 show an unexpectedly wide scatter of values, but do not support the hypothesis of an important sex-linked component in the genetic causation of the serum phospholipid level.

The correlation between mother and daughter is the lowest of the 4 and the sequence thereafter in order of increasing values is father and son, father and daughter, mother and son. None of these 4 correlation coefficients differs significantly from any of the others. The greatest difference is between the correlation coefficients for mother and daughter and mother and son, and this difference has a probability greater than .05 of having arisen as a result of sampling. We must, therefore, consider the variation among the 4 correlation coefficients as chance phenomena.

The absence of a correlation between the serum phospholipid levels of the parents and the presence of a significant positive correlation between the serum phospholipid levels of parents and child, and sibling and sibling are evidence of an important genetic component in the determination of serum phospholipid levels.

Relation Between Serum Cholesterol and Serum Phospholipid Level

The relation between serum cholesterol level and serum phospholipid level was determined from blood samples from 499 males and 510 females. There is a very high correlation between serum cholesterol and serum phospholipid levels in both males and females (.72 and .74 respectively, table 5). Within statistical limits, the correlation coefficients may be considered to be the same. The regression of serum phospholipid level on serum cholesterol level is statistically significant both for males and females. For each rise of 1 mg. per cent of serum cholesterol there is a rise of 0.72 mg. in males and 0.68 mg. in females of serum phospholipid. Within statistical limits these regression coefficients may be considered to be the same. In the light of the high correlation between serum cholesterol level and serum phospholipid level it is not surprising to find that the genetic analyses of these 2 variables parallel each other closely.[11]

Although high the correlation coefficients are considerably less than unity, hence a large amount of variation of the observed value about the predicted value of phospholipid level may be expected. A correlation coefficient of .72 accounts for only about 52 per cent of the variation around the mean, the remainder of the variation being due to sampling. Examination of the data for the 689 individuals in the 201 families in this study who were tested for serum cholesterol and serum phospholipid levels confirms this expectation. Ten had hypercholesteremia and hyperphospholipemia by our standards; 19 had hypercholesteremia, but not hyperphospholipemia; while 20 had hyperphospholipemia, but not hypercholesteremia. In each of the latter 39 individuals the "normal" value is in the upper range of normal.

Discussion

Only limited information is available concerning the influence of age, sex, environmental and hereditary factors on serum phospholipid levels of healthy persons. Almost no information is obtainable on levels in childhood and adolescence, or even among adults in significant numbers. Peters and Man[15] concluded that there was no effect of age and sex on serum phospholipid among 108 persons studied. Foldes and Murphy[17] reached the same conclusions. Gertler et al.[18] compared average phospholipid levels of normal control subjects and patients with coronary artery disease. They concluded that the difference between the 2 groups was significant, but did not evaluate their observation material

in regard to age and sex. Epstein et al.[15] could not discern a clear-cut trend in phospholipid levels in relation to age and sex. Lindholm[19] investigated serum lipids in 102 males and 93 females between the ages of 20 and 91. The phospholipid levels increased steadily with age in women, whereas in men this increase was seen only until age 50. Statistical criteria could not be applied to these data because of the small number of subjects. Table 6 summarizes the available information concerning serum phospholipid levels in normal persons.

Most investigators have been interested in serum phospholipid levels in disease, particularly atherosclerosis; in the relationship of serum phospholipids to cholesterol and other lipids; in influencing the level under experimental conditions; and in studies of phospholipid synthesis and turnover.

It has been shown that atheromatous plaques contain about 20 per cent phospholipid.[8] Serum phospholipid levels can be raised in animals by feeding cholesterol[20] and by injecting certain detergents,[21] and in man and animals by administration of steroid hormones.[22] Patients with atherosclerosis have, as a group, higher phospholipid levels than control subjects and higher cholesterol: phospholipid ratios.[18] It has been maintained that serum phospholipid stabilizes serum cholesterol and keeps it in solution.[23] It has been shown that the effect of certain (unsaturated) dietary fats on serum lipids is manifest in the lowering of serum cholesterol, and to a lesser extent of serum phospholipid.[24] Thus, more attention has been paid to the pathologic implications of phospholipid metabolism than to the variations of this lipid in the serum of healthy persons.

The present study indicates that serum phospholipid levels of healthy persons consuming a mixed diet increase with age in males earlier in life than in females. They are similar to the age-sex changes previously described for serum cholesterol, but of lesser magnitude. The levels of serum cholesterol and of serum phospholipid are distributed throughout this population as continuous variables. Our data also indicate the existence of a genetic factor determining serum phospholipid levels in healthy people.

TABLE 6.—*Serum Phospholipid Concentrations in Normal Persons**

Author	Yr.	No. & Sex	Age Range	Mean in mg./ 100 ml.
Boyd	1933	8 female	"young"	196
Page et al	1935	66 male	——	181
Peters and Man	1943	108 mixed	10-68	230
Foldes and Murphy	1946	20 mixed	20-35	228
		20 mixed	70-90	225
Kornerup	1950	73 male	19-96	173
		31 female	19-96	195
Ahrens	1950	20 mixed	21-38	219
Goldbloom	1952	15 mixed	22-72	218
Peterson	1952	21 male	20-55	208
		27 female	17-52	230
Swahn	1953	10 mixed	10-57	218
Gertler and Oppenheimer	1954	22 male	18-35	193
		22 female	18-35	228
		25 male	65-86	258
		25 female	65-86	258
Lindholm	1956	102 male	20-91	245
		93 female	20-91	252

*Adapted from data of Lindholm.[19]

The positive parent-child and sibling-sibling correlations and the negative mother-father correlations support the concept that serum phospholipid levels are genetically determined, probably in the same manner as serum cholesterol levels. These data further indicate that the common environment shared by a family does not lead to common serum phospholipid levels, unless blood relationship exists. Thus, such factors as diet cannot be the only factor in determining serum lipid levels of healthy persons.

On the basis of our admittedly limited data the responsible gene or genes are probably not sex-linked.

Hyperphospholipemia usually occurs in the presence of hypercholesteremia. A change of 1 mg. in serum cholesterol is accompanied by a change in the same direction of serum phospholipid amounting to 0.70 mg. Since this correlation occurs at all ages in both sexes a higher cholesterol: phospholipid ratio may be expected in hypercholesteremic than in normocholesteremic states. The importance of

the raised cholesterol : phospholipid ratio in atherosclerotic persons with hypercholesteremia is, therefore, open to question.

The problem arises as to the definitions of normophospholipemia and hyperphospholipemia. One is confronted here with a situation similar to that encountered in the definition of normocholesteremia and hypercholesteremia. Since serum phospholipid levels vary with age and sex, no single arbitrary line can be drawn between normal and elevated serum phospholipid levels. It is suggested, therefore, that the upper 5 per cent levels (table 3) of each age and sex group may be utilized for this purpose. Future studies will establish the possible clinical importance of such a delineation.

Summary

Serum phospholipid levels were studied in a healthy population sample in New York City including 1,067 persons, 516 males and 551 females, aged 2 to 77 years. Among these were 156 families consisting of 156 fathers, 156 mothers, and 268 children of these parents.

Serum phospholipid levels of healthy persons increase with age but in a different way for each of the 2 sexes. In males the level remains practically constant until age 20, rises sharply to age 32, and then remains constant until age 60. In females the level remains constant until age 32 and then rises gradually until age 60. These age-sex changes of serum phospholipid are similar to those observed for serum cholesterol but they are of lesser magnitude. The data indicate the existence of a genetic factor determining serum phospholipid levels in healthy persons.

A study of correlation coefficients of serum phospholipid revealed negative mother-father and positive parent-child and sibling-sibling correlations. These observations indicate that common environment in a family does not result in common serum phospholipid levels unless blood relationship exists, and that diet cannot be the only factor in determining serum phospholipid levels of healthy persons.

Because of the age-sex variations of serum phospholipid and serum cholesterol levels, no single arbitrary line can be drawn between normal and abnormally elevated levels of these 2 serum lipid fractions. The levels are distributed as continuous variables. The upper 5 per cent levels of each age and sex group may be utilized to characterize hyperphospholipemia and hypercholesteremia, respectively.

Summario in Interlingua

Le nivellos de phospholipido seral esseva studiate in un segmento representative de un population del Citate New York, incluse 1.067 individuos de sanitate normal, 516 masculos e 551 femininas, de etates de inter 2 e 77 annos. Se trovava inter illes 156 gruppos familial, i.e. 156 patres, 156 matres, e lor 268 pueros e pueras.

Le nivellos de phospholipido seral in individuos normal monta con le avantiamento del etate, sed non identicamente in le 2 sexos. In masculos le nivello remane practicamente constante usque al etate de 20 annos Postea illo monta acutemente usque al etate de 32 annos pro remaner de novo constante usque al etate de 60 annos. In femininas le nivello remane constante usque al etate de 32 annos e monta gradualmente usque al etate de 60 annos. Le variationes secundo sexo e etate in le nivellos de phospholipido seral es simile a illos observate pro cholesterol seral, sed lor magnitude es minor. Le datos indica le existentia de un factor genetic que determina le nivellos de phospholipido seral in individuos normal.

Un studio de coefficientes de correlation pro le nivellos de phospholipido seral revelava un correlation negative inter matre e patre e un correlation positive inter parente e progenie e inter fraterno e fraterno. Iste observationes indica que le milieu commun de un familia non resulta in commun nivellos de phospholipido seral, excepte sub conditiones de consanguineitate, e que le dieta non pote esser le sol factor in le determination del nivellos de phospholipido seral in individuos normal.

A causa del variationes secundo sexo e etate in le nivellos seral de phospholipido e de cholesterol, il non es possible fixar un sol linea de demarcation inter nivellos normal e supr-

ormal pro iste 2 fractiones lipidic del sero. n omne gruppo de etate e de sexo, le plus te 5 pro cento del mesurationes pote esser sate pro characterisar hyperphospholipemia hypercholesterolemia, respectivemente.

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Postural Hypotension

Variations in Different Drugs and Different Patients

By PHILIP L. DERN, M.D.

Clinical experience suggests that there are differences in the extent to which hypertensive patients respond with falls in blood pressure after administration of effective doses of ganglionic-blocking drugs. In this study attempts are made to define the relative magnitudes of the postural and nonpostural falls in blood pressure that are produced by these drugs. Frequent measurements of the blood pressure were made in hypertensive human subjects before and after the administration of ganglion-blocking agents. Drug-induced falls in blood pressure are calculated with reference to the baseline levels of blood pressure established in various ways for the individual patients.

IT IS well known that ganglion-blocking drugs produce postural hypotension. With some other drugs, for example reserpine, a drug acting mainly centrally, additional falls of blood pressure in the erect posture are usually inconspicuous. Claims have been made that some ganglion-blocking drugs may also have a central nervous system action. A major central effect is claimed for the drug IN 292 by Cavallito et al.[1] and Dontas and Nickerson[2] consider that hexamethonium acts partly at a preganglionic location. It was thought of interest to examine the extent of the postural and nonpostural falls of blood pressure induced by a number of ganglion-blocking agents with the idea that their relative magnitudes might differ if some of the drugs acted also on the central nervous system.

It was held in mind that postural hypotension is not confined to ganglion-blockers and that it occurs after nitrites, acting on smooth muscle, and after adrenolytic drugs. In contrast reserpine, canescine, and rescinnamine—rauwolfia alkaloids that appear to have a predominantly central action—cause postural hypotension only after very large doses. Whether this postural effect might be due to the peripheral musculotrophic effect demonstrated by McQueen, Doyle, and Smirk[3] is speculative.

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An additional reason for making a more extended study of postural hypotension is that most studies have not taken sufficient account of the time spent in the erect posture.

The formulas of the drugs studied are given in figure 1. It is noteworthy that mecamylamine differs from the others in being a secondary amine.

METHOD

The study of the relationship between falls of blood pressure that take place in the lying posture and the additional falls of blood pressure that occur on changing to the erect posture, following ganglionic blockade, become more complicated as attempts are made to obtain sufficient accuracy to justify a comparison of different ganglion-blocking drugs.

Correction for Postural Changes in Blood Pressure Present before Drugs are Given

1. If the control blood pressure in the lying posture is C_1 and the blood pressure in the lying posture during drug action is D_1, the fall of blood pressure in the lying posture (the after-drug nonpostural effect) is $C_1 - D_1$.

2. If C_s is the control blood pressure (systolic or diastolic) in the standing posture before drug administration then $C_1 - C_s$ = the "before-drug postural effect."

3. If D_s is the blood pressure (systolic or diastolic) in the standing posture before drug action then $D_1 - D_s$ is the additional fall of blood pressure, after the drug, on assumption of the erect posture. We call this the after-drug postural effect (uncorrected).

4. In determining the effect of drugs on postural induced falls of blood pressure it is desirable to correct for any postural changes that

m have been present before the drug is given. W en there is a fall of blood pressure on standing b re administration of the drug, $C_1 - C_s$ is p tive; when there is a rise of pressure on st ding, $C_1 - C_s$ is negative.

he difference between the after-drug postural eff t (uncorrected) and the before-drug postural eff t refers to the postural effect actually due to rug action = the after-drug postural effect (c rrected). This is: $(D_1 - D_s) - (C_1 - C_s)$.

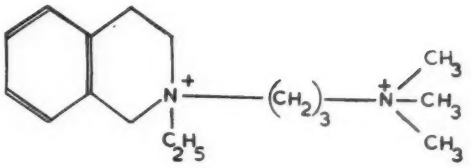
n representing the data graphs have been dr wn relating the nonpostural drug effect $(C_1 - D_1)$ to the after-drug postural effect, corrected $(D_1 - D_s) - (C_1 - C_s)$. It is considered that thi relationship is the most appropriate one to study. The formula may be written, alternatively, $(C_1 - D_s) - (C_1 - D_1)$. It could be argued that the subtraction of $(C_1 - D_1)$ is inappropriate as it appears in both the nonpostural drug effect and the after-drug postural effect corrected. The conclusions drawn are similar whether we relate the nonpostural drug effect $(C_1 - D_1)$ to the corrected $(C_s - D_s) - (C_1 - D_1)$ or alternatively to the uncorrected $(C_s - D_s)$ postural drug effect.

Selection of Representative Control Level of Blood Pressure

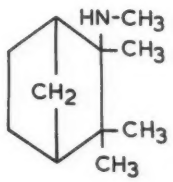
There is difficulty involved in the selection of a proper control level of the blood pressure from which the pressure may be said to fall as a result of drug action.

1. *Before-Treatment Control.* The casual blood pressure in the morning following several days of placebo administration may be used, and has the advantage that it is unaffected by the results of previous drug administration, a factor of importance, since some ganglion-blocking drugs, such as mecamylamine, produce effects lasting over 24 hours. An objection to the use of this "placebo control" is that it does not allow for any further downward drift in morning blood pressure readings that may occur during the study period and may be independent of drug action. This type of control is satisfactory for drugs administered on the day after the control period ends but may be too high a control value for drugs administered several days later.

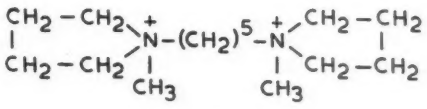
2. *Daily Control.* To avoid the above difficulty the blood pressure readings obtained on the day of each test, and just prior to the administration of drug, may be used alternatively as control values from which extent of the fall is estimated. An error due to persistence of drug effects from previous administration will be slight, but a lowering of the base line due to treatment, yet not to persistent drug action, cannot be eliminated altogether. The control values taken in this way, therefore, may be too low.



I.N. 292



Mecamylamine



Pentolinium

FIG. 1. Formulas of drugs.

For these reasons both the above types of control values of the blood pressure were used in calculating data. It will be seen that the conclusions drawn do not depend on which type of control is used.

Effect of Length of Time Spent in Lying and Standing Postures

The length of time spent in the lying posture or in the standing posture influences the results obtained. On assuming the erect posture, the blood pressure may show an initial drop followed by some recovery. If only one measurement of the blood pressure is made after standing it may not be representative. The technic used here was to make 6 measurements of the blood pressure at intervals of 30 seconds in the lying and standing postures. The averages of these blood pressures represent the "lying" and "standing" pressures at a particular stage of drug action. Several such sets of blood pressure readings were made in each patient during the action of each of the drugs studied, with the object of exploring the relationship of postural to nonpostural falls of blood pressure with varying intensities of drug action.

Administration of Ganglion-Blocking Drugs

Initially drug administration was by mouth—later, in order to have a better control over blood pressure levels, a number of experiments were

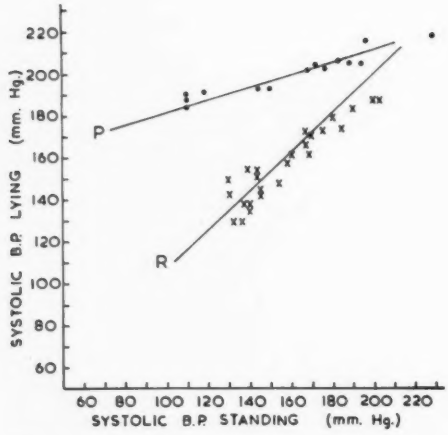


FIG. 2. The systolic blood pressure in the lying posture plotted against the systolic blood pressure in the standing posture. In series *P* the results were obtained from a patient given pentolinium on 2 days. In series *R* the values were obtained from a different patient given reserpine over several days (5.0 mg. per day).

made in which the drugs were given by injection. The route of injection had no significant effect on the results obtained. The amount of drug given was adjusted so as to reduce the blood pressure in the standing posture to normotensive or slightly hypotensive levels.

RESULTS

A simple graph relating the systolic blood pressures in the lying posture to those taken in the standing posture (fig. 2) shows that after moderately large doses of reserpine, the falls in the blood pressure are about equal in the lying and standing postures; but after pentolinium the falls of blood pressure are much greater in the standing posture.

The differences between the effects of the 3 ganglion-blocking agents to be studied (IN 292, mecamylamine, and pentolinium) were smaller than the difference between the effects of reserpine and of any one of these agents, and the more exact type of investigation mentioned earlier became necessary.

Observations Relating to Differences Between the Nonpostural Falls of Blood Pressure after Administration of Three Ganglion-Blocking Drugs. The relationships between the nonpostural and postural drug effects of IN 292, mecamylamine, and pentolinium are summarized in figure 3*A*–*F*. Figure 3*A*–*C* represents the relationship (systolic pressures) of the after-drug nonpostural fall of blood pressure to the after-drug postural fall (corrected), and figure 3*D*–*F* shows the corresponding relationship for diastolic pressures. In each case the before-treatment control referred to under "method" was used.

It will be seen that there is a difference between the effects of the 3 drugs on systolic and diastolic pressures. In each of the graphs the straight line at 45° from the zero point is drawn so as to pass through all points in which the nonpostural effect of the drug is equal to the postural effect. Where many points tend to lie to the left of this line, as in figure 3*A*, *D* (with the drug IN 292), it is evident that the fall of blood pressure in the lying posture often is greater than the additional fall of blood pressure that takes place on assumption of the erect posture. In contrast, when pentolinium is given (fig. 3*C*, *F*), most of the points lie to the right of the straight line, indicating that usually the postural fall of blood pressure exceeds the nonpostural fall. The position of mecamylamine (fig. 3*B*, *E*) seems to lie intermediate between IN 292 and pentolinium.

Additional graphs were prepared relating the after-drug nonpostural falls of blood pressure to the after-drug postural falls of blood pressure, but without correction for any postural falls or rises of blood pressure occurring under control conditions before drug administration. The graphs of uncorrected data are not reproduced as they are essentially similar to those of figures 3*A*–*F* (which are corrected).

It has been pointed out already that use of the before-treatment control tends to cause an overestimation of the falls of blood pressure due to drug action, whereas the "daily controls" (referred to under "method") may lead to an underestimate. The relationships between the nonpostural and postural drug effects of IN 292, mecamylamine, and pentolinium have therefore been analyzed with the use of "daily controls." The results are set out in figure 4*A*–*F*. The remarks made

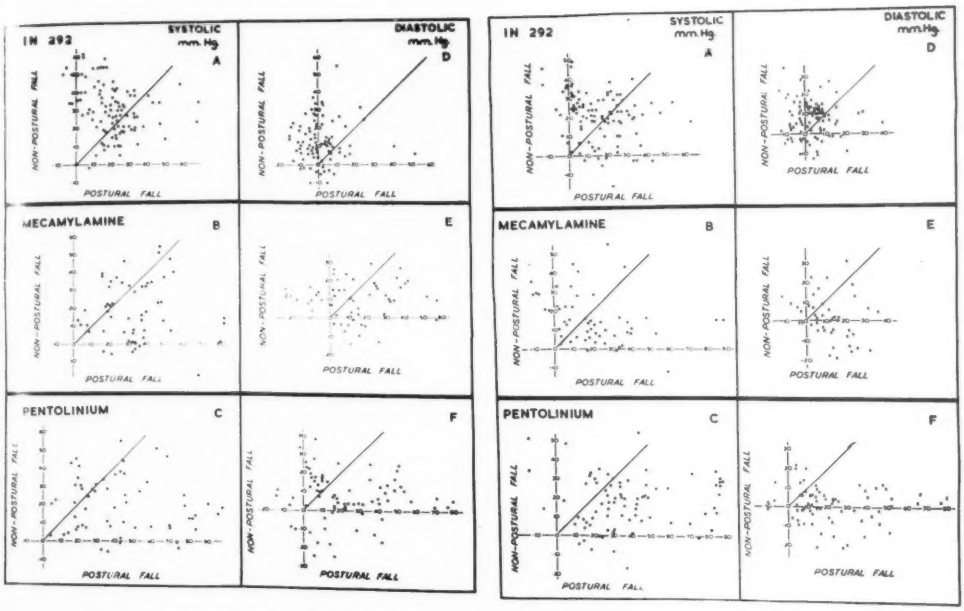


FIG. 3 *Left.* Data derived from 9 different hypertensive patients given IN 292 (*A* and *D*), mecamylamine (*B* and *E*), and pentolinium (*C* and *F*). For each drug the after-drug, nonpostural effect (C_1—D_1) plotted against the after-drug postural effect (corrected) (D_1—D_2) — (C_1—C_2). Pretreatment controls used for calculating magnitude of blood pressure falls.

FIG. 4 *Right.* Data derived from 9 different hypertensive patients given IN 292 (4*A* and *D*), mecamylamine (4*B* and *E*), and pentolinium (4*C* and *F*). For each drug the after-drug nonpostural effect (C_1—D_1) plotted against the after-drug postural effect (corrected) (D_1—D_2) — (C_1—C_2). Daily controls are used for calculating the magnitude of the blood pressure falls.

about figure 3*A*–*F*, apply equally to the analysis in terms of "daily controls."

It may be concluded that IN 292, relative to pentolinium, has more effect on the nonpostural falls of blood pressure whereas pentolinium, relative to IN 292, has more effect on postural falls of blood pressure. Mecamylamine occupies an intermediate position but resembles IN 292 more closely.

Since patients exhibit striking variations in their individual responses to a hypotensive drug, it is necessary to compare the effect of the drugs studied in the same individual. An example of a striking difference in the responses to different ganglion-blocking drugs is shown in figure 5. The other patients showed the same phenomenon to a greater or lesser degree.

It will be seen (fig. 5) that in this patient the after-drug nonpostural falls of blood pressure are relatively high after IN 292 and the after-drug postural falls of blood pressure are relatively high after pentolinium and mecamylamine.

Observations Relating to the Differences between the Nonpostural and Postural Falls of Blood Pressure in Different Individuals. There are differences between individual patients as well as differences between drugs. In the treatment of patients with ganglion-blocking drugs certain patients respond with large falls in blood pressure in the lying posture while others only exhibit appreciable falls of blood pressure on standing. In seeking an explanation for this variation it was noted that the response of a patient's blood

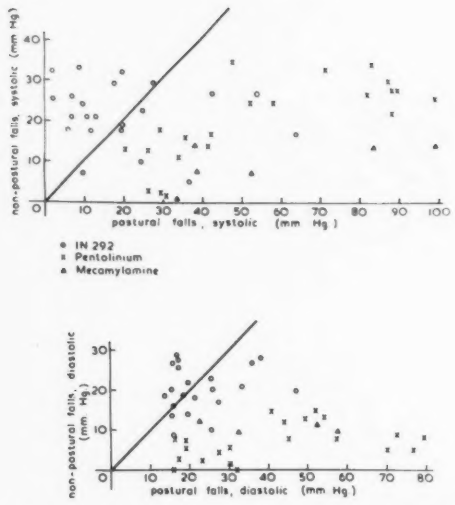


FIG. 5. A typical graph showing the responses of one female hypertensive patient (malignant hypertension) to IN 292, mecamylamine, and pentolinium. The after-drug nonpostural effect (C_1—D_1) is plotted against the after-drug postural drug effect (corrected) (D_1—D_s) — (C_1—C_s). For each drug various points are derived from measurements of the blood pressure at different times following drug administration.

pressure to standing prior to drug administration was related in an unexpected way to the magnitude of the postural response after a ganglion-blocking drug.

Relationship between the Magnitude of Postural Changes in the Blood Pressure before Giving a Ganglion-Blocking Agent and the Magnitude of the Postural Changes Afterwards. In figure 6 the before-drug postural falls of systolic blood presure (expressed as a percentage of the control blood pressure lying posture) are related to the after-drug postural fall, also expressed as a percentage of the control blood pressure lying posture.

The patients who had large before-drug postural falls in systolic blood pressure, paradoxically, tended to have small postural falls (fig. 6) but similar or possibly larger nonpostural falls. Those patients with before-drug rises in systolic or small falls in systolic pressure had relatively large postural falls

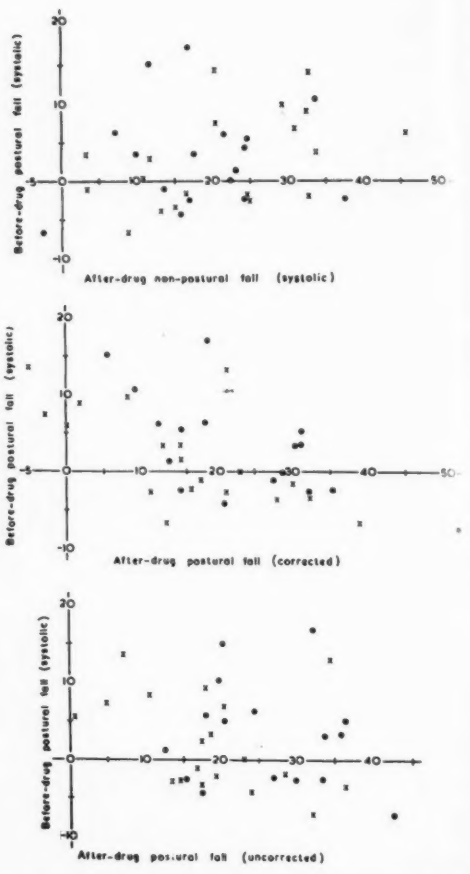

Before-drug postural fall (systolic)
After-drug non-postural fall (systolic)
Before-drug postural fall (systolic)
After-drug postural fall (corrected)
Before-drug postural fall (systolic)
After-drug postural fall (uncorrected)

FIG. 6. Relationship between the postural fall of blood pressure (systolic) before any ganglion-blocking drug was given and (1) the after-drug nonpostural fall, (2) the after-drug postural fall, corrected, (3) the after-drug postural fall, uncorrected. Each *point*, separate individual; *dots*, the author's personal observations; *crosses*, data obtained by technicians.

of blood pressure and similar or possibly smaller nonpostural falls during drug action. The relationship was clearly demonstrable whether the after-drug postural effect was corrected or uncorrected for postural changes in blood pressure present before drug administration. The control pressures used were those taken before any active drug had been administered. Corresponding results were obtained with the diastolic pressure.

Discussion

Clearly there are differences in the relative magnitudes of the nonpostural and postural falls in blood pressure induced by IN 292, mecamylamine, and pentolinium. It is notable that IN 292 tends to produce relatively marked falls of blood pressure in the lying posture, whereas the falls of blood pressure after pentolinium are more dependent on assumption of the erect posture.

No opinion is expressed about the possibility of relatively large nonpostural falls of blood pressure after IN 292 being related to the existence of a central nervous system action of the type suggested by Cavallito et al.[1] The topic deserves further study.

The observation that postural falls of blood pressure prior to receiving a drug are related to the magnitude of the postural fall of blood pressure after a ganglion-blocking drug is of interest. The patients with postural falls in blood pressure prior to drug action had, paradoxically, a tendency to small falls in blood pressure in the standing posture following drug action. A possible explanation is that a postural rise in blood pressure on standing in the absence of drug action represents an exaggeration of the compensatory reflex normally maintaining the level of the blood pressure on assumption of the erect posture; and that in patients with postural hypertension there is an increase in the neurogenically maintained fraction of the blood pressure (Doyle and Smirk[4]). Under these circumstances the administration of a ganglion-blocking drug should cause a larger fall of blood pressure. In the patients who had postural hypotension before receiving a ganglion-blocking drug it seems likely that the neurogenic response to assumption of the erect posture is insufficient to maintain the blood pressure level, and that the administration of a ganglion-blocking drug then causes a smaller fall of blood pressure because the neurogenically maintained part of the blood pressure is a smaller proportion of the whole.

O'Donnell[5] has described a variety of conditions that are likely to cause increases or decreases in the neurogenically maintained part of the blood pressure and lead to corresponding increases and decreases in the response to ganglion-blocking drugs.

Summary

1. Attention is directed to the need, when evaluating the magnitude of postural and nonpostural falls of blood pressure, to give consideration to (a) the time spent in the lying and standing postures, (b) the desirability of correcting for postural changes in blood pressure not dependent on drug action, and (c) the need to justify the choice of control blood pressure readings from which the blood pressure is said to fall.

2. There are differences in the relative magnitudes of the postural and nonpostural falls in blood pressure produced by IN 292, mecamylamine, and pentolinium. IN 292 produced large falls in blood pressure not dependent on the assumption of the erect posture, whereas pentolinium produced mainly postural effects.

3. Paradoxically, patients demonstrating postural rises in pressure under control conditions prior to receiving ganglion-blocking drugs tend to have large postural falls in pressure following the action of these agents. A possible explanation is discussed.

Acknowledgment

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Summario in Interlingua

1. Es signalate le necessitate, in evaluatar le magnitude del reduction postural e nonpostural del pression de sanguine, de prender in consideration (a) le tempore passate in position jacente e in position erecte, (b) le desirabilitate de effectuar correctiones pro alterationes postural in le pression de sanguine le quales non depende del action de un droga, e (c) le necessitate de justificar le selection del pression de controlo ab que le reduction es mesurate.

2. Il existe differentias inter le magnitudes relative del reductiones postural e non-postural del pression de sanguine effectuate per IN 292, mecamylamina, e pentolinio. In 292 produceva forte reductiones del pression de sanguine non dependente del prender un postura erecte, durante que pentolinio produceva principalmente effectos postural.

3. Paradoxemente, patientes con augmentos postural del pression sanguinee sub conditiones de controlo ante le administration de drogas a blocage ganglionic tende a exhibir forte reductiones postural del pression sanguinee post le action del agentes mentionate. Un explication possibile de iste phenomeno es discutite.

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Wolferth, C. C., Fitts, W. T., Jeffers, W. A., and Sellers, A. M.: The Place of Adrenalectomy in the Treatment of Severe Arterial Hypertension. Bull. New York Acad. Med. **33**: 151 (March), 1957.

One hundred sixty-eight patients with blood pressures of over 200/120 mm. Hg were subjected to partial or total adrenalectomy alone or in combination with various forms of sympathectomy. One hundred eighteen of the patients have lived and 50 died over the observation period from 3 months to 8 years. Forty-eight patients have responded with blood pressures in the range of 150/100 mm. Hg and 27 with blood pressures below that. Improvement in funduscopic examination has occurred in these patients. In 55 there was improvement in the electrocardiogram and decrease in heart size during the follow-up period. Blood urea nitrogen determination was a reliable index for renal function. In 70 of the 118 patients headache was a major complaint before operation, and in 62 patients the headache was relieved or disappeared entirely. Thirty-six of the survivors of adrenalectomy developed some pigmentation of the Addisonian distribution. Eight patients developed recognizable peptic ulcer. All patients with total adrenalectomies were treated with replacement cortisone and desoxycorticosterone acetate. In hot weather supplementary salt was given.

The authors believe that fully 50 per cent of individuals with severe hypertensive disease subjected to adrenalectomy and sympathectomy exhibit a total improvement, that this type of operation is quite justified, and that the results obtained by these procedures are rarely equaled by the administration of antihypertensive drug therapy. The authors point out that there is no successful procedure for selecting patients capable of a highly favorable response to the operation. At the present time they limit the operation to those in urgent need of control of hypertensive disease or those who respond poorly to antihypertensive drugs or who are unable to tolerate antihypertensive drugs.

Harvey

Ventricular Activation in the Pre-Excitation Syndrome (Wolff-Parkinson-White)

By Robert P. Grant, M.D., Fred B. Tomlinson, A.B., and James K. Van Buren, A.B.

Seventy cases of pre-excitation were studied by vector translating methods. Certain properties of the delta event are described that are useful in the recognition of this syndrome electrocardiographically. In about half the cases a ventricular conduction defect without QRS-interval prolongation was demonstrated to have accompanied the pre-excitation. The type of ventricular conduction defect produced depended upon the particular direction of spread of the pre-excitation wave. This and other findings are incompatible with the hypothesis that pre-excitation is due to accelerated atrioventricular conduction and favor the hypothesis that it is due to bridges, whether morphologic or electronic, between atria and ventricles.

TWO SYNDROMES have been described that are characterized by a short P-R interval in the electrocardiogram and a predilection for paroxysmal tachycardia. Both have been called the Wolff-Parkinson-White syndrome. In one, the P-R interval is only apparently shortened, for there is an abnormal deflection immediately preceding and fusing with the QRS complex accounting for the shortened P-R interval. The abnormal deflection, called the "delta wave," is due to premature activation of a region of ventricular myocardium and therefore this has become called the "pre-excitation" type of Wolff-Parkinson-White syndrome.[1] In the other, less common type the P-R interval is absolutely shortened, there is no delta wave, and the QRS complex is normal in contour and duration. It may be called the "Lown-Ganong-Levine" type after the authors who most completely described it.[2] The present study is concerned only with the pre-excitation type of this syndrome.

Although many case reports of pre-excitation have been published there has been no systematic, controlled study of the electrocardiographic changes that take place in this syndrome. Seventy cases of pre-excitation have been collected in which tracings had been recorded during normal conduction as well as during pre-excitation. By the use of vector-translating methods to compare the normal and the pre-excitation tracings, it has been possible to study some of the properties of the electric forces responsible for the delta waves and to examine the extent to which excitation of the remainder of the ventricular myocardium is affected by pre-excitation. The findings shed light on the probable mechanism of this syndrome in man.

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Material and Methods

Twenty-eight personal cases were augmented by an additional 42 cases from the literature with satisfactory tracings during both pre-excitation and normal conduction. No cases were accepted that showed alternating pre-excitation, since one could not be sure that the abnormal complexes were not simply premature ventricular contractions. The method for plotting spatial vectors from the conventional clinical tracings has been described previously.[3] For each case the frontal plane projections of the QRS loop during normal conduction and during pre-excitation (a delta-plus-QRS loop) were plotted, the same scale being used for both loops. In addition, the spatial direction of the mean delta vector was plotted from the delta waves in the various leads of the pre-excitation tracing.

The method for studying the extent to which QRS forces had been altered by pre-excitation was as follows. First, several instantaneous vectors were drawn on the QRS loop plotted from

the tracing of normal conduction (fig. 1). These instantaneous vectors were next drawn on the delta-plus-QRS loop with exactly the same magnitudes and directions that they had for the normal loop, the terminus of each instantaneous vector being placed at the appropriate instant on the QRS part of the delta-plus-QRS loop. The vector at a given instant during the writing of the delta-plus-QRS loop is the sum of the delta electric force and the QRS electric force generated at that instant. Therefore, when the instantaneous QRS vectors of the normal loop are translated to the delta-plus-QRS loop, the location of the *origin* of each vector is also the terminus of a delta vector, if one is being generated at that instant. By drawing a line through the origins of the translated QRS vectors a loop is formed that indicates the variation in magnitude and direction of the electric force generated from instant to instant by the pre-excitation wave. This is called a "delta loop." Delta loops were plotted by this method in each case. However, they could be considered accurate in a given case only if there had been no change in the direction of the QRS vectors as a result of pre-excitation, i.e., that there was no ventricular conduction defect with the pre-excitation. This could be determined by studying the size and shape of the loop plotted for a given case. There are several reasons for believing that the delta loop is narrow, with little variation in the direction of the electric force from instant to instant during the delta event. In the first place, the portion of the delta loop that precedes the writing of the QRS complex is always narrow. This is well shown in cases demonstrating the "concertina" effect, where there is progressively more delta wave preceding the QRS complex from deflection to deflection or from tracing to tracing in a given patient. Several excellent examples of this have been published in the literature illustrating the essentially monophasic contours of the delta waves on the various leads.[1, 4, 5] In the second place, it has been shown in previous studies that when ventricular excitation travels outside the conduction system of the ventricles, as in right and left bundle-branch block, the portion of the loop written by this phase is always narrow.[6] Finally, there are a number of cases of pre-excitation which, when the pre-excitation tracing is compared with normal conduction tracings, are clearly due to perfectly normal QRS complexes superimposed on monophasic delta waves, and in these cases the delta loop is always narrow and small; figure 1*B* is an example. From these considerations it was concluded that when the plot of the delta loop was unusually large or bizarre in contour, it probably was not a true delta loop, and the QRS vectors must have been changed in direction by pre-excitation to account for the bizarre loop. This is, of course, an indirect method for deciding whether or not pre-excitation had caused a ventricular conduction abnormality. Further-

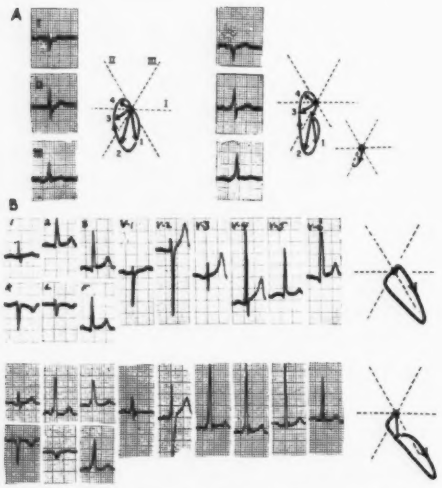

FIG. 1. Two cases of pre-excitation with control tracings. *A, left,* standard limb leads and frontal plane projection of the QRS loop during normal conduction; instantaneous vectors have been drawn on the loop for 4 instants during the QRS interval. *A, right,* the same leads during pre-excitation. The arrow-tipped interruption of the initial limb of the delta-plus-QRS loop in this and subsequent figures identifies the portion of the loop written solely by delta forces. The 4 vectors of the control loop have been translated to the appropriate instants of the delta-plus-QRS loop. The origins of translated QRS vectors 1 and 2 lie on the delta part of the loop, indicating that the delta forces generated before and after QRS forces begin to appear have essentially the same magnitudes and directions, i.e., the delta loop is narrow. Vectors 3 and 4 have origins at the zero point of the triaxial figure, indicating that the delta event had subsided by that time. The plot of the frontal plane projection of the delta loop is shown at the right; the initial, solid limb written by delta forces generated before QRS forces appear, and the terminal, dotted limb written by those generated after QRS forces appear. *B, above,* tracing and frontal plane QRS loop during normal conduction. *B, below,* during pre-excitation. The QRS parts of the deflections have essentially the same contours in both tracings, indicating that the delta vectors are essentially parallel in direction throughout the delta interval. The QRS vectors of the first .01 to .02 second of the QRS interval are less superiorly directed during pre-excitation than during normal conduction, and this is the only part of the QRS sequences that has been measurably altered by pre-excitation.

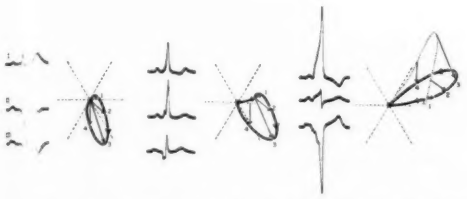

FIG. 2. *Left.* Standard limb leads and frontal plane projection of the ventricular loop during normal conduction. *Center.* During one stage of pre-excitation. *Right.* At a later stage of pre-excitation. The 4 instantaneous vectors plotted on the normal loop are translated to the other 2 loops without changing the magnitudes or directions of the vectors. For the middle tracing, the origins of the translated vectors lie along the pathway of the delta part of the loop, while for the tracing on the right, the origins of the translated vectors describe a pathway (dotted line) that is bizarre in contour and large in size. This cannot be the loop of delta forces and a ventricular conduction defect must have accompanied this stage of pre-excitation. (Tracings copied from Eichert, Annals of Internal Medicine 21: 907, 1944).

more, slight changes in ventricular conduction sequences cannot be detected by this method. Only those cases where the changes were marked were used for the analysis of the ventricular conduction defect seen with pre-excitation.

The method is illustrated by the cases in figures 1, 2, and 3. In the first case of figure 1, the delta forces are at first perpendicular to the lead I axis then point slightly rightward. When the 4 instantaneous vectors of the normal loop are superimposed on the pre-excitation loop it can be seen that their origins define an exceedingly narrow loop. The second case in this figure is another example where, even without the vector plot, the pre-excitation complexes can be seen to be formed by normal QRS complexes simply superimposed on monophasic delta waves for each lead. The contours of the QRS complexes during pre-excitation so closely resemble the normal complexes that there can have been little alteration in the sequences of ventricular depolarization in these cases and therefore the plot of the delta loop must be relatively accurate in both. Note that in the first case, the instantaneous QRS vectors are displaced from the zero point of the trivial figure for only the first half of the QRS cycle. This means that the delta event lasted only for the first .04 second of the QRS interval. This case illustrates how the duration as well as the resultant magnitude and direction of the delta electric event can be measured in a given case using vector translating methods.

In figure 2 are shown 3 tracings from one subject. The 3-stage sequence illustrated here was encountered in 3 cases of the present series but in none were the tracings available for reproduction, and the deflections in this figure were copied from a case reported by Eichert.[7] When instantaneous vectors of the normal QRS loop are translated to the loop for the second tracing, it can be seen that their origins define a small narrow delta loop indicating that there can have been little alteration in ventricular conduction as a result of this stage of pre-excitation. However, when the instantaneous vectors are translated to the loop for the third tracing, their origins define a large and bizarre pathway (dotted line) that cannot plausibly be considered to be defining delta vectors. Indeed, some parts of this loop are larger than the QRS loop itself. It is concluded that the sequences of ventricular depolarization were altered by this degree of pre-excitation, producing a left axis deviation of the QRS vectors. Figure 3 illustrates the other common type of ventricular conduction defect associated with pre-excitation. When the instantaneous QRS vectors of the normal tracing are translated to the loop drawn for the pre-excitation tracing in this case, their origins define a large and bizarre loop (dotted line) that cannot be a definition of delta vectors because it is so large. Furthermore, it defines rightward vectors, which is an exceedingly improbably direction for the vectors of the delta event. It is concluded that a ventricular conduction defect must have accompanied pre-excitation in this case, resulting in right axis deviation of the QRS vectors during pre-excitation.

Results

The Delta Event

In the 70 cases, the mean vector calculated for the portion of the delta event that preceded the QRS forces had the range in direction shown in figure 4. Thirty-two or nearly half the cases had a mean delta vector that was horizontal or leftward in direction, 16 or less than one fourth were inferior or even rightward in direction, and 22 or slightly more than a fourth had a direction between these 2 extremes. The series is of course a selected one, including only those cases in which tracings with normal conduction were also available, and it may not accurately represent the true incidence of different delta vector directions in pre-excitation.

It might be wondered if this variation in frontal plane direction of the delta vector might not be simply due to different electric

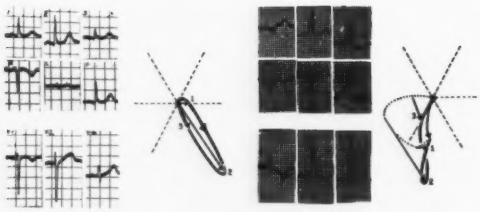

FIG. 3. *Left.* Conventional leads and frontal plane projection of the ventricular loop during normal conduction. *Right.* During pre-excitation. When the instantaneous vectors of the normal loop are translated to the loop during pre-excitation, their origins define a large loop (dotted line) with bizarre contour that cannot be due to delta forces, indicating that a ventricular conduction defect accompanied pre-excitation.

positions of the heart. This was tested by comparing the direction of the mean QRS vector of the control tracing with the direction of the delta vector during pre-excitation in all cases. There proved to be the same incidence of vertical and horizontal electric positions of the heart among cases with a leftward delta vector as among cases with an inferiorly directed vector. The different directions of the delta vector must be due to differences in direction of spread of the delta event in the ventricles rather than to differences in the electric or anatomic position of the heart.

It will be noted that when the delta vector is leftward in direction it writes a negative deflection on lead III (as in the second tracing of fig. 2) and, if markedly leftward, on lead II as well. Under these circumstances the initial take-off of the delta-plus-QRS complex on leads II and III closely resembled the Q_2 and Q_3 of diaphragmatic infarction, and several cases have in the past been erroneously called diaphragmatic infarction because of this resemblance. Similarly, when the delta vector is rightward and inferior in direction (as in fig. 3), it writes negative deflections on lead I and lead aV_L which have occasionally been confused with Q_1 and Q_L of anterolateral infarction.

In the past, pre-excitation has been divided into types A and B depending upon whether V_1 has an initial positive or negative deflection during pre-excitation. In the present series of cases the delta vector was more or less parallel with the frontal plane of the body in 90 per cent of cases, pointing only slightly anteriorly or posteriorly from this direction from case to case. When it pointed slightly posteriorly, the V_1 electrode location was now in the area of negativity for this vector direction and recorded an initial negative deflection. When it was directed slightly anteriorly, V_1 was now in the area of positivity, writing a positive delta wave. Thus, whether or not V_1 had a positive or a negative delta wave depended upon only slight differences in the anteroposterior direction of the delta vector in most cases, and is not a critical factor in differentiating cases of pre-excitation. Much more valuable for cataloging cases of pre-excitation is the direction of the delta vector in the frontal plane, for this appears to determine the type of ventricular conduction defect that might appear.

Two calculations of the magnitude of delta vectors were made for each case. One calculation was made from the portion of the delta event that preceded QRS events, called the manifest delta vector, and the other was made from the maximal amplitude of the entire delta loop, when this could be reliably plotted, called the mean delta vector. In the frontal plane, the manifest delta vector varied from 2 to 10 mm. in magnitude, and the mean delta vector was as much as 15 mm. in amplitude. This means that the delta wave in a given limb lead may account for as much as 15 mm. of the amplitude of the delta-plus-QRS complex. Anteroposteriorly, its magnitude was often considerably greater. In those cases where the manifest delta vector was anteriorly directed its projection on V_1 was from 4 to 8 mm. and that of the mean delta vector as much as 25 mm. From the practical clinical point of view this means that pre-excitation must be considered whenever the initial R wave at V_1 is unusually tall or broad.

In a very small proportion of cases the delta vector had a different direction from those shown in figure 4. For example, in 3 cases the mean delta vector was directed markedly anteriorly. The delta loop was

relatively narrow spatially in these cases, but because of the anterior direction its projection on the frontal plane was wide. The case in figure 5 illustrates this point. Here the QRS complexes have smaller amplitude during pre-excitation than during normal conduction, an uncommon occurrence in pre-excitation. The explanation for this lies in the peniform shape of the frontal plane projection of the delta loop, with much of it lying in the region of the triaxial figure, which is negative for the 3 standard limb leads. With the normal instantaneous QRS vectors originating from this region of the triaxial reference figure, the magnitude of positivity they project on the axes for the 3 limb leads is reduced, and this accounts for the reduced amplitude of the limb lead QRS complexes.

The pre-excitation events persist through only the first half of the QRS interval in this case, for the second half of the QRS complex on the various leads (and the second half of the QRS loop) has essentially the same size and contour in the pre-excitation tracing as during normal conduction. The duration of the delta event could be reliably measured only in those cases in which there was no ventricular conduction defect during pre-excitation. In over 80 per cent of these cases the pre-excitation event could be identified during only the first .04 second of the QRS interval. This plus the portion of pre-excitation that preceded the QRS events gave pre-excitation a total duration of .07 to .08 second in most cases. In none could it be shown to persist throughout the QRS interval or to extend beyond the end of the QRS interval. This confirms the generally accepted opinion that the delta event is due to depolarization of ventricular myocardium.

QRS Events

There was an unexpectedly high incidence of cases with little or no detectable change in the direction or duration of QRS forces when pre-excitation developed, 35 of the 70 cases being of this type. That QRS forces were unchanged was often not obvious from a "pattern" point of view. For example,

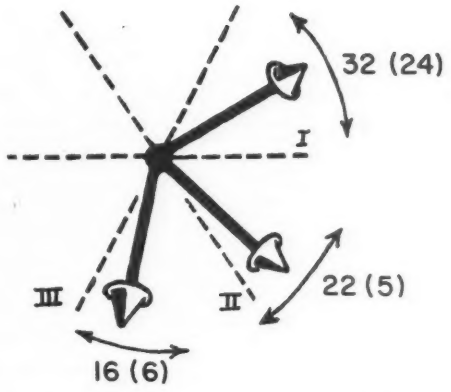

FIG. 4. Distribution of directions of the mean delta vector in 70 cases of pre-excitation. The first number indicates the number of cases with the indicated general direction of the mean delta vector; the number in parentheses indicates the number of cases in each group with a significant ventricular conduction defect during pre-excitation. The mean delta vectors are drawn as if they all were slightly anteriorly directed. This applied to only 50 per cent of each group; the others were plumb with the frontal plane or even directed slightly posteriorly.

if the delta vectors were inferior in direction, the origin of QRS vectors would now be shifted to an area on the triaxial figure where they would project negatively on lead I and the delta-plus-QRS complex would now be largely a negative deflection on this lead, whereas it was a positive deflection prior to the development of pre-excitation. This is illustrated by the first case in figure 1. Likewise in cases with markedly leftward delta vectors, the zero point for the QRS forces was often shifted to the negative region of the triaxial figure as far as the lead III axis is concerned causing the normally directed QRS vectors to write a more negative QRS complex on this lead during pre-excitation than they did during normal conduction.

Among the cases with changed directions of QRS vectors during pre-excitation the direction of the delta vector appeared to be the principal factor determining whether or not the QRS vector change would take place. For example, in the cases with leftward delta vectors, over two thirds showed changes in the directions of the QRS vectors (i.e., a ventricular conduction defect appeared during the

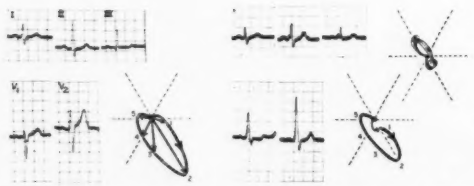

FIG. 5. *Left.* Tracings and frontal plane projection of the ventricular loop during normal conduction. *Right.* During pre-excitation. The plots of the translated vectors on the delta-plus-QRS loop are not drawn on the figure for reasons of clarity; however, their instants are numbered, and above is shown the 3-dimensional plot of the delta loop defined by the pathways of origins of the translated vectors.

pre-excitation syndrome in these cases). On the other hand, among the cases in which the delta vector was directed inferiorly and rightward, only a third showed changes in the directions of QRS vectors; and among the cases with an intermediate direction of the delta vector less than one fourth showed a measurable change in direction of QRS vectors with pre-excitation (fig. 4).

Furthermore, the type of directional change which the QRS vectors were caused to take was also a function of the direction of the delta vector. Among the 32 cases with leftward delta vectors, 24 showed QRS vector alterations and 22 of these developed marked left axis deviation of the QRS vectors (third tracing of fig. 2). On the other hand, among the 16 cases with the delta vector directed inferiorly, 6 showed QRS vector changes and 5 of these developed right axis deviation of the QRS vectors (fig. 3). Only 5 of the 22 cases with intermediate delta vector direction had detectable QRS vector alterations; 3 developed some degree of the leftward type of conduction defect and 2 the rightward type.

While 85 per cent of cases with QRS vector changes developed either a marked left or a right axis deviation, other types of QRS alteration were occasionally seen. For example, among the cases where the amplitude of the delta event increased from tracing to tracing (the "concertina effect") the QRS components often became smaller and smaller without change in contour or duration. The increasing amplitude of the delta waves could usually be attributed to the fact that pre-excitation started earlier and earlier after the P wave, permitting a longer period of time for pre-excitation to invade the myocardium. The reduction in magnitude of the QRS forces when this took place is perhaps due to the fact that, as more myocardium was depolarized by the pre-excitation event, less was left for depolarization by the normal atrioventricular impulse. This type of alteration differed from the others in that there was no change in the direction of the instantaneous QRS vectors as they became reduced in magnitude. In certain other cases the directions of QRS vectors for just the first .01 to .02 second of the QRS interval were altered by pre-excitation. This suggests that not infrequently the pre-excitation wave may invade the region of the ventricles that is normally first to be depolarized, the endocardial layers of the septal and paraseptal regions of the left ventricle.

An unexpected finding was the rarity with which prolongation of the QRS part of the delta-plus-QRS interval was encountered. This was surprising in view of the fact that this syndrome was once called the "syndrome of short P-R interval with QRS prolongation." In recent years it has been recognized that much of the apparent prolongation of the QRS interval was due to the delta wave, but the notion that the QRS component is abnormal in contour and duration has persisted to the present day. Among cases of this series where accurate measurement of QRS components was possible, a measurable degree of prolongation of the QRS part of the delta-plus-QRS complex was seen in less than 10 per cent of cases, and in none was it prolonged by more than .03 second. Certain cases showed QRS prolongation in serial tracings of pre-excitation,[1] but it is possible that the administration of quinidine may have been responsible for it.

DISCUSSION

Half of the 70 cases of pre-excitation studied in this series showed little or no alteration of the QRS vectors during pre-excitation. This means that pre-excitation cannot have greatly affected the spread of ventricular ac-

tivation in these cases. However, the delta event is due to depolarization of ventricular muscle and the electric energy contained in the delta event therefore must be removed from the QRS forces that follow. Why does this change not substantially alter the magnitudes or direction of the QRS vectors? The answer perhaps lies in the observations of Scheffer,[8] who showed that no more than 10 per cent of the electric energy generated by ventricular depolarization is manifested in the normal QRS complex, with the other 90 per cent canceled out by simultaneous activation of oppositely located regions of the ventricles. There are probably no oppositely located regions undergoing activation during the pre-excitation event and therefore, by analogy, perhaps no more than 10 per cent of the delta wave is removed from the QRS events to follow it, an amount too small to detect with conventional methods of recording. Furthermore, it has been suggested that there is normally no resultant electric activity produced by activation of the subendocardial layers of the left vetricle.[9] The delta vector appears to be in part at least due to activation of subendocardial layers, and while not all workers are in agreement that the subendocardium is electrically "silent,"[10, 11] if it were, then pre-excitation might not significantly subtract from the manifest QRS forces that follow it.

In fact, since the pre-excitation event is due to a relatively small electric force, it is surprising that QRS forces are ever altered in this syndrome. Nevertheless, half the cases of this series showed marked QRS changes during pre-excitation. It was found that the particular direction of the delta vector played an important role in determining whether or not QRS changes would take place and the type of QRS change that would be produced. For example, three quarters of the cases with leftward and superiorly directed delta vectors developed QRS changes, while in the cases with leftward and inferiorly directed delta vectors QRS changes were infrequent (fig. 4). Furthermore, among the cases that developed QRS vector changes, when the delta vector was leftward and superiorly directed (left axis deviation of the delta vector), the QRS vectors also showed marked left axis deviation; in contrast, when the delta vector was inferior or rightward in direction, right axis deviation of QRS vectors took place (figs. 2 and 3).

Before an explanation for these observations is suggested, it should be recognized that in most cases the change in the directions of the QRS vectors was unassociated with measurable QRS prolongation. It had formerly been thought that ventricular conduction defects were always associated with prolongation of the QRS interval. However, this is the fourth example so far identified of a ventricular conduction defect in man in which there may be no QRS prolongation. The first to be proved in man was peri-infarction block, where the QRS vectors generated during the second half of the QRS interval are changed in direction by the infarction, and the direction they take is a function of the electric location of the myocardial infarction.[12] The second is the $S_1S_2S_3$ syndrome associated with myocardial infarction. In this the electric location of the infarct is immaterial: it is seen particularly in patients with somewhat rightward terminal QRS vectors prior to the infarct, as if there were a vulnerability of right ventricular conduction in these patients.[12] The third type is less definitively proved than the other two; however, there is considerable circumstantial evidence that uncomplicated left axis deviation of more than −30 degrees without QRS prolongation is a left ventricular conduction defect, most commonly due to myocardial fibrosis such as is seen in advanced left ventricular hypertrophy, arteriosclerotic heart disease, etc.[13] In support of the concept that these are all ventricular conduction defects, in spite of the normal duration of the QRS interval, is the demonstration that left axis deviation and other QRS complex abnormalities without QRS prolongation can be produced in the dog by lesions in certain regions of the left ventricular conduction system distal to the left main bundle.[14]

The explanation for the normal QRS interval duration in these conduction defects is be-

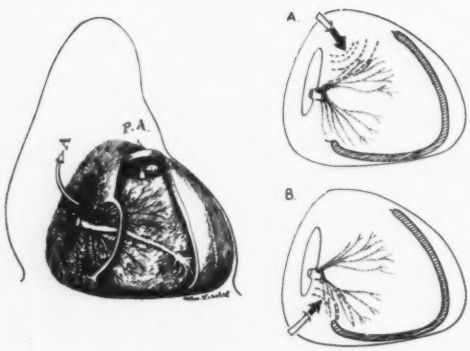

FIG. 6. *Left.* Schema of the ventricular conduction system. The ventricular heart is shown as viewed frontally, with the free wall of the right ventricle partially removed. Right and left bundles are shown as if the septum were transparent. *Right.* 2 sites of entrance of the pre-excitation impulse are suggested. *A*, when pre-excitation enters from a superior region, its wave of depolarization spreads inferiorly soon encountering branches of the superior division of the left bundle. *B*, when pre-excitation enters from an inferior region of ventricular myocardium, its wave spreads superiorly soon encountering branches of the inferior division of the left bundle.

lieved to be related to the anatomy of the left ventricular conduction system, schematically shown in figure 6. The left bundle divides into 2 major groups of fibers, one traveling superiorly and the other inferiorly, and the 2 divisions join peripherally forming a conduction syncytium. It is suggested that if a lesion involves many fibers of one of these divisions, excitation will spread via the other division with an alteration in the sequences of ventricular depolarization, but little or no prolongation of the QRS interval. According to this hypothesis the QRS interval is prolonged by conduction defects only when there is no alternative route in the ventricular conduction system for excitation to follow, for now excitation must travel by the much slower mechanism of intramyocardial spread. This is believed to be the explanation for the QRS prolongation in right and left bundle-branch block.

When pre-excitation is associated with a change in QRS vector direction, either left axis deviation of −30 to −60 degrees or right axis deviation of +80 to +110 degrees is produced and other directional changes are rarely seen. These same 2 alternative vector directions are seen in the vast majority of cases of peri-infarction block, suggesting that perhaps the 2 divisions of the left bundle play a role in pre-excitation similar to that ascribed to them in peri-infarction block.[12]

These features of pre-excitation lead to the following hypothesis to explain the ventricular conduction defects in this syndrome. It is postulated that in the majority of cases of pre-excitation a stimulus from the atrium crosses the atrioventricular ring into the interventricular septum giving rise to the pre-excitation event, and this stimulus may enter at any of a number of different points in the septum. If it enters near the diaphragmatic margin of the septum (B of fig. 6), the pre-excitation wave will spread leftward and superiorly, producing a leftward and superiorly directed delta vector. With this direction the wave will soon reach the territory of the inferior division of the left bundle; if it reaches these fibers before the normal atrioventricular impulse is delivered to the ventricular conduction system, the ventricles will be depolarized from below upward via the left ventricular conduction pathway syncytium, producing left axis deviation of the QRS vectors without QRS prolongation. On the other hand, if the pre-excitation starts at the upper margin of the septum (A of fig. 6), its direction of spread will be inferior, producing an inferiorly directed delta vector. It spreads toward the territory of the superior division of the left bundle, and if it reaches these fibers before the normal atrioventricular impulse enters the ventricular conduction system, ventricular depolarization will be from above downward within the conduction pathway syncytium, producing right axis deviation of the QRS vectors without QRS prolongation. Then, if pre-excitation should start at a point in the septum between these 2 extremes it will spread leftward and inferiorly producing a leftward and inferior delta vector; but with this direction it would enter both divisions of

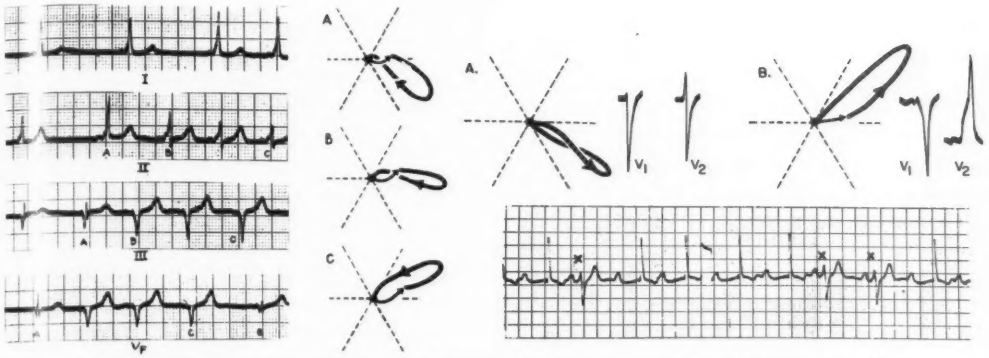

FIG. 7 *Left.* Case of pre-excitation with sinus arrhythmia. With slight variations in the P-R interval varying degrees of disturbance of ventricular conduction result. Delta-plus-QRS loops A, B, and C were constructed from complexes labeled with the same letter.

FIG. 8 *Right.* Intermittent pre-excitation illustrating P-R interval prolongation of the normaliy conducted beats and normal P-R interval duration of the pre-excitation beats (×). Lead II only is shown. Frontal plane projections of the normal loop and the delta-plus-QRS loop are shown constructed from the limb lead tracings, *A*, during normal ventricular conduction, *B*, during pre-excitation.

the left bundle nearly simultaneously and there would be no change of the QRS vectors. This hypothesis explains why certain delta vector directions are more frequently associated with QRS vector changes than others, and why the directions the QRS vectors take is specific for that delta vector direction; it also explains why, with a relatively small part of the ventricles involved in pre-excitation, QRS vector changes are so common; and it explains why there may be no prolongation of the QRS interval with the QRS vector changes.

It follows from this hypothesis that whether the QRS vectors will be normal or not in a given case of pre-excitation will often depend upon the duration of the P-R interval, for this will determine whether the pre-excitation wave or the normal atrioventricular impulse will be the first to enter the ventricular conduction system. Perhaps this is the explanation for the "concertina" effect that Giraud was able to record in many patients with pre-excitation by taking tracings serially immediately after exercise.[5] With the tachycardia of exercise, the P-R interval is always slightly shortened. Therefore, when patients with pre-excitation are exercised, the normal atrioventricular impulse would tend to reach the ventricular conduction system before the more slowly traveling pre-excitation wave, resulting in normal QRS forces. Then, with rest and slowing of the heart rate, the P-R interval would return to its normal longer duration; as a consequence the pre-excitation wave would reach the ventricular conduction system before the normal atrioventricular impulse, resulting in changes in the directions of QRS forces. This role of the P-R interval duration may also explain why many patients with pre-excitation have normally directed QRS forces during episodes of paroxysmal tachycardia, and why atropinization will often normalize the QRS vectors in patients with pre-excitation. Figure 7 illustrates this when the cause for the slight variation in P-R interval is a marked sinus arrhythmia. With the longer P-R intervals (C complexes), the delta wave is larger in magnitude and deformity of QRS forces greater than with the shorter P-R intervals (A complexes).

These observations also shed light on the probable mechanisms of pre-excitation in man, supporting the theory that it is due to anomalous connections between the atria and the ventricles (whether these connections are morphologic, such as the Bundles of Kent, or electrotonic as Sodi-Pallares suggests[15]) and

tending to be incompatible with the theory of accelerated conduction along fibers of the atrioventricular node.[16] In the first place, the delta wave spreads so slowly in the heart that, however it is initiated, its propagation cannot be along conduction fibers and must be by intramyocardial spread of activation. In the second place, for a leftward delta force to cause left axis deviation of the QRS vectors it must enter the septum low enough preferentially to invade the inferior division of the left bundle, while for an inferiorly directed delta vector to produce right axis deviation it must enter the septum high enough preferentially to invade the superior division. These 2 locations are too far apart anatomically to be attributable to fibers in or adjacent to the atrioventricular node. In fact, the wide variation in direction of the delta vector in the frontal plane in pre-excitation (fig. 4) is itself strong evidence against any theory that postulates the same site of entrance of pre-excitation into the ventricles for all cases. To explain these events by accelerated nodal conduction would require postulating that the atrioventricular impulse could be conducted to widely separated parts of the ventricles where it leaves the conduction pathways only to reenter them again in the appropriate division of the left bundle, a sequence of events which by its very complexity is improbable. Finally, the case shown in figure 8 indicates that under certain circumstances conduction through the atrioventricular node may play no part whatever in the pre-excitation syndrome. In this tracing during normal atrioventricular conduction the P-R interval has a duration of nearly .40 second, while during pre-excitation the QRS vectors are generated only .16 second after the P wave. Other, though less striking, examples have been published in the literature.[17] Ventricular conduction must be entirely due to the pre-excitation wave in this case, for it is unlikely that both abnormally accelerated and abnormally delayed conduction could be present simultaneously in the atrioventricular node. It will be noted that there is a ventricular conduction defect without prolongation of the QRS interval in this patient during pre-excitation, and this is perhaps as nearly proof as one is likely to find in man that in certain patients with pre-excitation the abnormal QRS sequences must be related to the pre-excitation wave itself and not to any aspect of atrioventricular nodal conduction.

Several workers have tried to identify the point of origin of the delta wave, using intracavitary electrocardiographic leads.[5, 18] Unfortunately, it is often overlooked that deflections recorded within the chambers of the heart obey the same laws regarding the distribution of potential in a volume conductor as do deflections recorded outside the heart or on the body surface, and intracavitary deflections have therefore often been overinterpreted. A positive delta wave in the right ventricle, for example, does not necessarily mean the delta vector is pointing toward the right ventricle. It means only that the recording electrode lies in the half of the body toward which the delta vector is directed; the delta vector may have any direction through 180 degrees to write a positive deflection at any given electrode position. Nevertheless the published intracavitary findings are compatible with the hypothesis that leftward delta vectors arise from an inferior region of the ventricular mass while inferiorly directed delta vectors arise from a superior region of ventricular muscle mass.

There are, no doubt, still other mechanisms to account for the QRS changes in the pre-excitation syndrome in addition to that postulated above. For example, it has been repeatedly shown that pre-excitation complexes can be produced during right heart catheterization. In the only study of this phenomena so far published where precordial V leads were taken simultaneously with the intracavitary leads, the delta vector proved to be pointing nearly directly posteriorly (i.e., negative delta waves in all the precordial leads).[5] This is the direction of spread one would expect of an impulse starting from the septal surface of the right ventricle, and is a direction that is rarely seen in spontaneous pre-excitation.

Summary and Conclusions

Seventy cases of pre-excitation with tracings during pre-excitation and during normal atrioventricular conduction have been studied by vector translating methods.

The spatial direction of the mean delta vector was examined. The practice of dividing cases of pre-excitation into types A and B from the direction of the delta wave at V_1 proved to depend upon a trivial difference in the direction of the delta vector, for in the vast majority of cases the delta vector was more or less parallel with the frontal plane of the body.

In half of the cases the directions of QRS forces were altered by pre-excitation, indicating that a ventricular conduction defect accompanied pre-excitation in these cases. The conduction defect was unassociated with prolongation of the QRS part of the pre-excitation complex. The type of conduction defect that develops depended upon the direction of spread of the pre-excitation wave in the ventricles. An explanation for the conduction defect is suggested, based upon the bi-divisional architecture of the left ventricular conduction network.

A case of pre-excitation with P-R interval prolongation of normally conducted beats is presented. This case and other findings in the study cannot be explained by the accelerated atrioventricular conduction theory of pre-excitation, and favor the theory of anomalous bridges (morphologic or electrotonic) between atrial and ventricular myocardium.

Summario in Interlingua

Septanta casos de pre-excitation con registrationes in pre-excitation e in conduction atrioventricular normal esseva studiate per methodos de traduction vectori.

Le direction spatial del vector delta medie esseva examinate. Esseva constatate que le practica de divider casos de pre-excitation in typo A e typo B super le base del direction de unda delta in V_1 depende de un differentia trivial in le direction del vector delta, proque in le grande majoritate del casos le vector delta esseva plus o minus parallel con le plano frontal del corpore.

In un medietate del casos, le directiones del fortias de QRS esseva alterate per pre-excitation. Isto indica que in tal casos un defecto in le conduction ventricular accompania le pre-excitation. Le defecto de conduction non esseva associate con prolongation del parte QRS del complexo de pre-excitation. Le typo del defecto de conduction le qual se disveloppava dependeva del direction del diffusion del unda de pre-excitation in le ventriculos. Es proponite un explication del defecto de conduction, basate super le architectura bipartite del rete de conduction sinistro-ventricular.

Es presentate un caso de pre-excitation con prolongation del intervallo P-R in pulsos a conduction normal. Iste caso, e etiam altere constatationes del presente studio, non es explicabile per la theoria de un acceleration del conduction atrioventricular in pre-excitation. Le observationes supporta plus tosto le theoria del exesitentia de pontes anormal (morphologic o electronic) inter le myocardios atrial e ventricular.

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So Nature being perfect and divine, and making nothing in vain, neither gave a heart to any where there was no need, nor made it before there was any use for it, but by the same degrees in the forming of all animals passing through the constitutions of all creatures (as I may in the egg, Worm, and birth) it acquires its perfection in them all.—William Harvey. *De Motu Cordis*, 1628.

A Study of the Manifestations of Rheumatic Fever Following Cessation of Therapy

By EDWARD E. FISCHEL, M.D., CHARLES W. FRANK, M.D., AND MARJORIE T. BELLOWS, M.S.

Following cessation of therapy for acute rheumatic fever manifestations of rheumatic activity frequently reappear. The incidence of these manifestations and their severity were studied during the 3-week observational period in 257 patients treated as part of the Cooperative Clinical Trial on the treatment of rheumatic fever. From the analysis of these manifestations certain concepts may be derived concerning diagnostic and therapeutic criteria.

WHEN hormone or salicylate therapy for acute rheumatic fever is discontinued there is frequently a reappearance or persistence of manifestations of rheumatic activity. These have been variously interpreted.[1-3] Exacerbation of the disease following withdrawal of salicylate therapy was described in 1876,[4] when salicylate was introduced as an antirheumatic drug. With the use of adrenal corticoids more attention has been focused on this phenomenon. Although the manifestations of rheumatic activity are frequently transient and subside spontaneously, the benign aspects of this phenomenon have perhaps been overly emphasized. Attempts have been made to differentiate between the mild and severe exacerbations using the terms "rebound" and "reactivation." Such differentiation can be made only in retrospect. The post-therapy reactions are manifestations of rheumatic activity emerging after the discontinuation of suppressive therapy. Their severity seems to be related to the severity and duration of the preceding rheumatic attack. Study of this phenomenon may also contribute to the formulation of broader diagnostic and therapeutic concepts.

The records of 257 children treated in the United States and Canada in the Cooperative Clinical Trial of ACTH, Cortisone, and Aspirin,[5] were made available for this analysis by agreement of the principal investigators of that study. It is thought that these data afford a unique description of the post-therapy period, inasmuch as all the children were kept in the hospital for 3 weeks following 6 weeks of therapy. Regular observations of the commonly accepted indices of rheumatic involvement were recorded.

Because the current analysis is concerned with the description of the post-therapy period, the data from all 3 treatment groups have been combined. Cardiac murmurs have not been included as indices of "activity," since changes in intensity are difficult to evaluate, and new murmurs did not occur during this period. The signs observed are listed in table 1. Abnormal erythrocyte sedimentation rates of 20 mm. or more (uncorrected Wintrobe method) occurred in one half of the patients. Fever, defined as at least 2 consecutive days of rectal temperature over 100.3 F. or 1 day over 101.3 F., was recorded almost as frequently. The other manifestations in order of frequency were P-R interval greater than 0.18 second, joint involvement manifested by arthralgia or arthritis, erythema marginatum, congestive failure or pericarditis, nodules, and chorea.

Of the 257 children, one quarter had none of the above manifestations of rheumatic activity during the 3 weeks following therapy, and the others had 1 to 5 manifestations (table 2).

These 8 manifestations appeared in 35 dif-

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TABLE 1.—*Incidence of Specific Manifestations*

Manifestation	Patients	
	Number	Per cent
Fever	114	44.4
Erythrocyte sedimentation rate	130	50.6
P-R interval over 0.18 second	37	14.4
Joint involvement	23	8.9
Failure or pericarditis	10	3.9
Erythema marginatum	13	5.1
Nodules	9	3.5
Chorea	2	0.8
No manifestations	67	26.1
Total patients	257	100.0

TABLE 2.—*Number of Manifestations of Rheumatic Fever per Patient*

Number of manifestations per patient	Number of patients	Per cent
None	67	26.1
1	90	35.0
2	65	25.3
3	25	9.7
4	7	2.7
5	3	1.2
Total patients	257	100.0

ferent combinations, forming a wide spectrum of severity. Many of the combinations of signs that occur during the post-therapy period would not be specific enough to establish a diagnosis of rheumatic fever without knowledge of the earlier course. This observation suggests that inadequate or abortive initial therapy may obscure later attempts at diagnosis.

The number of manifestations exhibited during the post-therapy period varied with the cardiac status on admission, there being more manifestations with more severe initial involvement. In table 3 the 257 children are grouped according to the cardiac status at the start of therapy. The first 2 groups represent first attacks of rheumatic fever, with or without carditis. Children with prior heart disease are next listed. Finally, 33 children with failure or pericarditis are presented, three fourths of whom were in their first known attack.

There was also a great number of manifestations during the post-therapy period in those patients who were first treated 6 weeks or more after the onset of their illness (table 4). It is not known whether this increase is due to the selective factor of late therapy itself or to other factors. There is no difference between the groups treated 0 to 14 days from onset and those treated 14 to 42 days.

These data suggest several interpretations concerning the significance of the post-therapy period. The apparent relationship between the duration and severity of the rheumatic process before therapy and the frequency with which abnormalities appear after withdrawal of therapy is again indicative of the relationship of the "rebound" to the basic disease. If the "rebound" were solely a drug-induced phenomenon, unrelated to rheumatic fever, such a relationship would not be expected.

The importance of the post-therapy exacerbation during its acute phase is dramatically apparent in those few patients, 4, who first experienced cardiac failure or pericarditis at that time. One of these patients died, despite prompt reinstitution of therapy. Six patients had a recurrence or continuation of failure and pericarditis during the period following therapy.[5] In some instances the severity of the disease during the post-therapy period was as great or greater than at the start of treatment. In most instances, the various abnormalities subsided spontaneously. Retreatment was considered necessary for only 6 patients. It is difficult to assess the contribution of the rebound to the development of permanent valvular or myocardial damage. Under the conditions of therapy, prophylaxis, and 1 year follow-up of the Cooperative Clinical Trial, it appears that in most instances no effect could be attributed to the recurrence of inflammatory reaction after discontinuation of therapy. Nevertheless, the extent of heart damage may be related to the severity and duration of rheumatic inflammatory reaction, whether this occurs before, during, or after suppressive therapy. Just as it appears judicious to avoid recurrent attacks of rheumatic fever by prophylaxis, so it may be of value to avoid exacerbations of rheumatic in-

TABLE 3.—*Cardiac Status at Start of Therapy*

Cardiac status	Total cases	Per cent with number of manifestations			
		Total	0	1 or 2	3 or more
carditis, no pre-existing heart disease	76	100.0	35.5	59.2	5.3
rditis present, no re-existing heart isease	104	100.0	23.1	66.3	10.6
e-existing heart isease	44	100.0	20.5	54.6	25.0
ilure or pericarditis	33	100.0	21.2	51.5	27.3
Total	257	100.0	26.1	60.3	13.6

flammation at any time. Appropriately designed therapeutic programs may eliminate or minimize the recurrence of inflammatory reaction.[3, 6] This approach may be of particular importance in the management of those patients with cardiac involvement or illness of long duration, in whom a recurrence of inflammation may be more likely to occur.

From the nature of the rebound we may also deduce some of the areas in which the drugs had an effect, however incomplete. When any or all of the presenting manifestations of rheumatic activity subside during drug therapy, the effect may be attributed to several possible causes: spontaneous remission in the course of the disease, bed rest, or to the drug administered. Following cessation of therapy, the recurrence of rheumatic manifestations is ample evidence that the drug employed did not eradicate the disease. However, it is also evidence, in retrospect, that the drug had a suppressive action while it was being administered. It was widely taught that aspirin did not affect the rheumatic inflammation in the heart (and that concept has occasionally been extended to cortisone). The recurrence of heart failure or pericarditis after cessation of either drug conflicts with that view. A flare-up of the disease process would not be expected if a totally ineffective agent were discontinued.

SUMMARY

The 3-week period following cessation of therapy was studied in 257 children with rheumatic fever treated for 6 weeks as part of the Cooperative Clinical Trial.[5]

Most patients exhibited some manifestations of rheumatic activity, most frequently an elevation of the erythrocyte sedimentation rate or of temperature. Occasionally more severe and complex manifestations occurred. The number of manifestations was greater in those patients with more severe manifestations on admission.

The study of the post-therapy period may provide some perspective concerning diagnostic criteria and the effectiveness of therapeutic agents in retrospect. The manifestations of the post-therapy period are sufficiently common under apparently good conditions of management. Study of this period should be included in attempts to define optimal therapy for rheumatic fever.

TABLE 4.—*Duration of Rheumatic Fever before Start of Therapy*

Duration before therapy	Total cases	Per cent with number of manifestations			
		Total	0	1 or 2	3 or more
0—14 days	146	100.0	28.1	61.6	10.3
14—42 days	59	100.0	33.9	55.9	10.2
43 + days	52	100.0	11.5	61.5	26.9
Total	257	100.0	26.1	60.3	13.6

SUMMARIO IN INTERLINGUA

Durante 3 septimanas immediatemente post le cessation del tractamento, observationes esseva colligite in 257 patientes pediatric con febre rheumatic qui habeva essite tractate durante 6 septimanas como parte del Essayo Clinic Cooperative.[5]

Le majoritate del patientes exhibiva alicun manifestationes de activitate rheumatic, le plus frequentemente un acceleration del sedimentation erythrocytic o un elevation del temperatura. In alicun casos, plus sever e complexe manifestationes esseva notate. Le numero de iste manifestationes esseva plus grande in le patientes in qui le manifestationes habeva essite le plus sever al tempore de lor hospitalisation.

Le studio del periodo post-therapeutic provide possibilemente un certe perspectiva concernente le criterios diagnostic e le efficacia

del agentes therapeutic (judicate in retrospecto). Le manifestationes del periodo post-tractamental es satis commun sub apparentemente bon conditiones de providentia. Le studio de iste periodo debe esser includite in tentativas de definir optimos therapeutic pro febre rheumatic.

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Medical Eponyms

By Robert W. Buck, M.D.

De Musset Sign. The de Musset sign of aortic regurgitation was described not by a physician, but by Paul de Musset, brother of the poet, in his "Biography of Alfred de Musset" *(Biographie de Alfred de Musset, sa Vie et ses Oeuvres)* Paris, 1877. The quotation is from chapter 14, pages 274-275.

"The illness so well cared for by Sister Marcelline had left him with a troublesome tendency to affections of the chest. . . .We called the doctors twice during the course of the winter; they bled him too often.

"Whatever they may say, I am convinced that their lancets caused him irreparable harm. At breakfast one morning in March, I noticed that my brother's head was bobbing involuntarily with each pulse beat. He asked my mother and me why we were looking at him with such a startled air. We told him what we saw, and he said, 'I did not think you could see it; but I will reassure you.'

"He made some sort of pressure on his neck with his index finger and thumb, and in a moment his head stopped marking his pulse. 'You see,' he then said to us, 'that this dreadful illness can be cured by simple and inexpensive means.'

"We were reassured, being ignorant, for we had just observed the first symptom of a grave malady to which he was to succumb fifteen years later."

Nonpenetrating Traumatic Injury of the Heart

By Loren F. Parmley, Lt. Col., MC, William C. Manion, M.D. and Thomas W. Mattingly, Brig. Gen., MC

The misconception that nonpenetrating trauma to the heart is relatively rare, is primarily due to the fact that myocardial contusion or traumatic pericardial lesions are usually well tolerated and the clinical findings transient and often difficult to recognize. However, the sequelae of this type of cardiac trauma may be serious. Therefore, a careful evaluation of every traumatized individual for cardiovascular injury is essential if the more serious complications are to be recognized and treated effectively. The most commonly encountered cardiac lesion at necropsy was myocardial rupture of a septum or a chamber wall. Now that surgical therapy is available for certain types of cardiac rupture, early diagnosis is essential. Thrombosis of a major coronary artery as a direct result of nonpenetrating trauma was not found in this study and is considered rare. Nevertheless, a previously diseased heart appears to be more vulnerable to trauma. Under these circumstances, it is often difficult to assess properly the extent to which trauma may aggravate a pre-existent disease.

IN THE present era of high-speed transportation and mechanization of industry, injuries that result in trauma to the heart and great vessels are on the increase. While direct injuries of the penetrating type are usually readily recognized and appropriately handled, the etiologic relation of nonpenetrating and indirect injuries to cardiac trauma is often overlooked, either at the time of injury or when complications are latent. This, despite the fact that there are many excellent reports[1-7] on nonpenetrating cardiac injuries, Warburg's contributions[8, 9] being the most comprehensive. The true incidence of nonpenetrating traumatic injuries to the heart and the morbidity and mortality rates still are not well established. As a consequence, medical and legal opinions in such matters may be arbitrary and conflicting.

It is the purpose of this paper to discuss the causation and to present pathologic data on 546 autopsy cases of nonpenetrating traumatic injury to the heart, and to review our clinical experience with the problem by presenting selected case studies. The 546 cases from the files of the Armed Forces Institute of Pathology represent 0.1 per cent of a total of 207,548 autopsy cases that were available for study. This low incidence is comparable to that reported by others.[10, 11]

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Cause

The mechanisms whereby nonpenetrating injuries to the heart may be produced have been described.[1, 2, 12, 13, 14] The forces that cause these injuries may be placed empirically in 7 broad categories: (1) direct, (2) indirect, (3) bidirectional or compressive, (4) decelerative, (5) blast, (6) concussive, and (7) combined. Only a few of these warrant discussion.

Indirect force produces an increase of intravascular hydrostatic pressure such as occurs with sudden compression or crushing of the abdomen and extremities. This mechanism of trauma has been demonstrated experimentally by Beck and Bright.[13] The most frequently cited clinical example of cardiac rupture due to indirect forces is the case reported by Kellert.[15] A similar case is included in our series.

Blast forces resulting in visceral injury have been well defined.[14] Several instances of rupture of a ventricle, interventricular septum, or both, caused by blast trauma were found in our series.

Concussion of the heart, as Beck[2] admitted, is an empirical term. Nevertheless, it is descriptive and may be used to indicate forces

TABLE 1.—*Lesions Found in 546 Autopsy Cases of Nonpenetrating Trauma to the Heart Tabulated According to the Predominant Lesion and Showing in Parentheses the Number Whose More Significant Associated Cardiac Injury Was Tabulated in Another Category*

Type and/or Site of Injury	Number of cases	Cases combined with Aortic Rupture	Total
Rupture	273	80	353
Right ventricle	56	10	66
Left ventricle	46	13	59
Right atrium	35	6	41
Left atrium	24	2	26
I.V. septum	25(20*)	5(4*)	30
I.A. septum	18(10*)	7(3*)	25
Multiple chamber ruptures	69	37	106
Contusion/Laceration	105	24	129
Pericardial Laceration	18	18	36
Hemopericardium	13	12	25
Valvular Laceration/ Rupture	1(2†)	0(4†)	1
Aortic	1(1†)	0(2†)	1
Pulmonary	0(4†)	0	0
Tricuspid	0(8†)	0	0
Mitral	0(8†)	0(1†)	0
Mitral & tricuspid	0(1†)	0(1†)	0
Coronary artery Lac/Rupture	0(7†)	1(2†)	1
Papillary muscle Lac/Rupture	1(23†)	0	1
Total	411	135	546

*Associated with other sites of cardiac rupture.

†Combined with cardiac rupture or other cardiac injury.

that, although of no great magnitude, are sufficient to produce sudden jarring of the heart. Perhaps vagosympathetic responses or direct interference with the neuromuscular mechanisms of the heart result in cardiac standstill or ventricular arrhythmias in the more serious cases. Characteristically, if death is the outcome, significant lesions of the myocardium may not be found. Experimentally this was noted by Schlomka,[16] who produced ventricular tachycardia and fibrillation in experimental animals when he traumatized the heart by direct blows, yet could not demonstrate significant anatomic changes in the myocardium at necropsy. Kissane and Koons[4] duplicated these results. It was their impression that a region of increased irritability was produced whether or not hemorrhage could be demonstrated. Whatever the mechanism, clinical examples of injury of this type that resulted in sudden death have been reported,[17] and there are 2 in our autopsy series. The first individual died a few minutes after he was hit in the chest by a stick; the second was struck in the precordium by a pitched ball, took a few steps forward and fell dead. On postmortem examination, neither showed evidence of cardiac injury other than a few petechiae, primarily in the epicardium, and no other pathologic changes to explain death.

INCIDENCE

The incidence of nonpenetrating traumatic injury to the heart can only be estimated, because the mortality rate is low and the morbidity generally minimal. The incidence reported in autopsy[18–20] and clinical series[21] has varied from 10 to 75 per cent in the presence of severe trauma, especially chest injury. When the lower percentage is used as an index, the incidence of cardiac injury from automobile accidents alone in the United States is in the range of 150,000 of the population annually. However, the cardiac injury is often overlooked by the clinician, for other bodily injury often masks the manifestations of cardiac trauma which, in most instances, must be searched for immediately after injury if they are to be discovered. Recognition of the early signs of cardiac injury is important, so that proper clinical safeguards can be instituted to minimize complications and to insure prompt and efficient treatment should the more serious sequelae develop.

PATHOLOGY

The principal lesions encountered in the autopsy series of 546 cases of nonpenetrating traumatic heart disease are presented in table 1. In the majority, the injury to extremities or other parts of the body was so severe that the patient would have died in the absence of cardiac lesions.

The results of the important experimental work of Moritz and Atkins,[22] Bright and Beck,[3] and Kissane and co-workers,[4, 23] have been analyzed in an attempt to correlate them

ith our observations on autopsy and clinical aterial. One of the more significant facts ecovered by these investigators was that di- ct nonpenetrating cardiac trauma seldom oduces serious consequences unless the my- ardium is ruptured or fatal arrhythmia velops. Study of the myocardium in these imals, even a few days after production of ntusion, revealed little if any pathologic idence of trauma. Lesions similar to those oduced experimentally in animals have been monstrated by many investigators, includ- ng ourselves, to be relatively incidental in tally injured persons. If they had survived eir other injuries, the cardiac lesions prob- bly would have caused little morbidity, and aling would have been as complete as in the perimental animals.

Gross description of the lesions in our se- ries, while ample in most cases, was brief and sketchy in some, leaving uncertainty as to ex- tent and location. In many, records of the exact time of injury and death of the victim allowed computation of the interval during which the morphologic changes took place. Attempts to correlate these changes with the time sequence were not very fruitful because of the variety of causative forces, as well as the effect of other associated injuries, many of them severe. It was possible, however, to select from the material a series of lesions that differed in the extent to which they in- volved the heart and pericardium. While some of these lesions were single, often more than one was present, including associated cardiac lesions such as pericardial laceration with myocardial hemorrhage. The lesions were classified as follows:

- Parietal pericardial hemorrhage
- Parietal pericardial lacerations
- Hemopericardium
  - Acute
  - Organizing
- Pericarditis
- Cardiac hemorrhage or contusion
  - Subepicardial
  - Myocardial
  - Subendocardial
- Lacerations and contusions
- Rupture of the heart

Parietal Pericardial Hemorrhage. Hemorrhage into the parietal layer of the pericardium occurred as an isolated lesion or group of lesions. It was often associated with other traumatic lesions of the adjacent mediastinal structures and heart. Hemorrhagic manifestations varied from small punctate hemorrhages to large hematomas several centimeters in diameter. Grossly the small lesions must be distinguished from the so-called agonal hemorrhages frequently seen on the surface of the heart and pericardium in the absence of a history of trauma. Microscopic examination revealed hemorrhage into the fibrous connective tissue stroma of the pericardium, but the mesothelial lining of the inner surface often remained intact (fig. 1*A* and *B*).

Parietal Pericardial Lacerations (249 Cases). Lacerations of the parietal pericardium were either superficial or penetrating. The superficial lacerations involved the external or internal surface of the pericardium and sometimes were associated with hemopericardium or other evidence of injury to the heart. In 18 cases pericardial laceration was an isolated lesion (table 1). Lacerations were single or multiple, and varied in length from a few millimeters to 10 cm. or more. In some cases disruption of the pericardial sac was so extensive that the lesion was best described as rupture, the heart often being found in one of the pleural cavities. When descriptions of the site of the lesion were available, it was more often on the left side; but in many cases accurate localization was impossible.

Hemopericardium. Hemorrhage into the pericardial sac was frequently observed. It occurred as the only lesion in 13 cases (table 1). In the acute form associated with the fatal lesions, the pericardial sac was distended with blood, which often was partially clotted. The source of hemorrhage could usually, but not always, be demonstrated. The microscopic findings varied with the duration of the hemorrhage. If there had been a period of survival after the injury, both the parietal pericardium and the epicardial surface were coated with a layer of organizing hemorrhage (fig. 1*C*, *D*, and *E*).

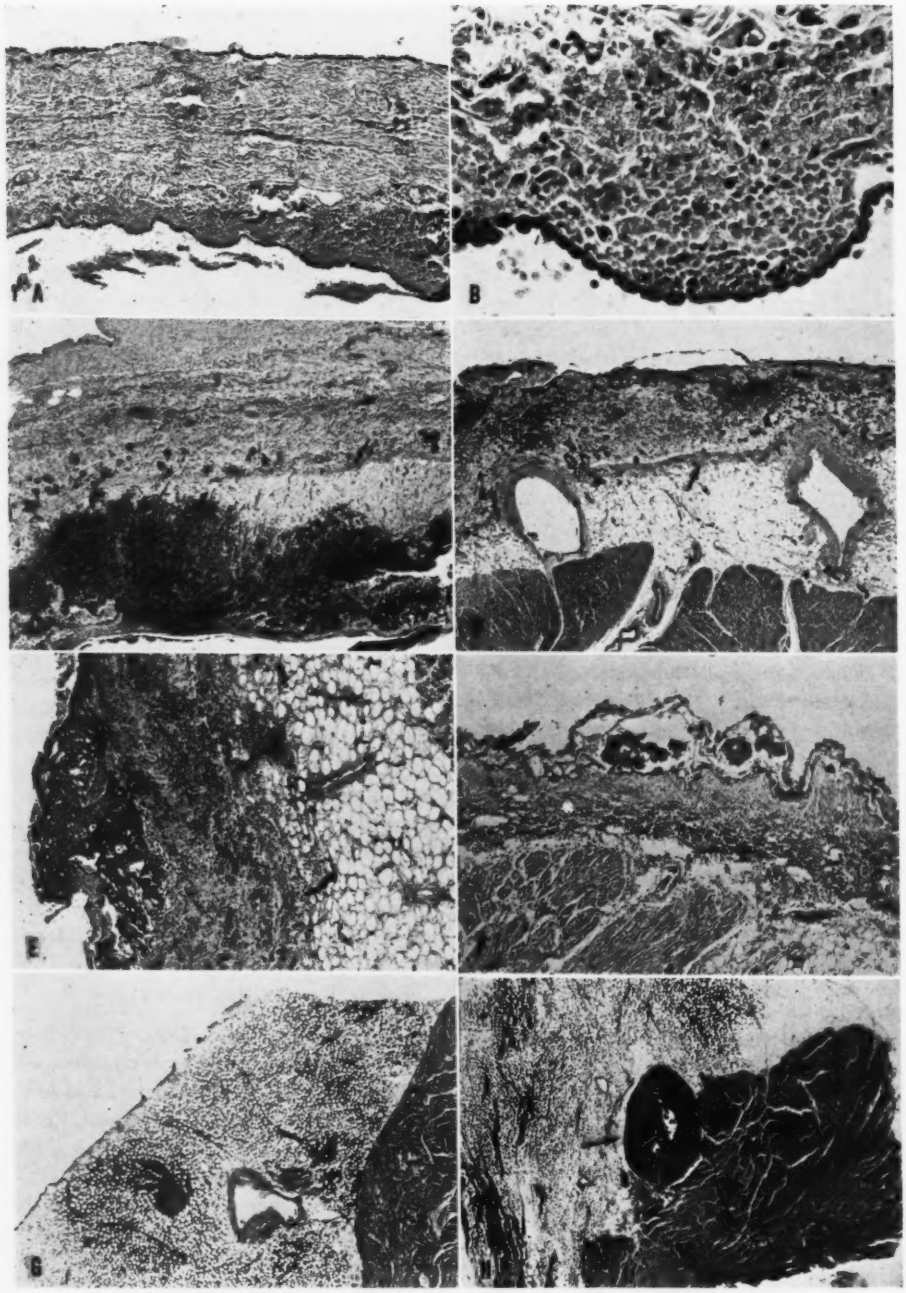

FIG. 1. *A*. AFIP Acc. 727325. Parietal pericardial hemorrhage. × 35. *B*. Higher power of part of the same field, showing the intact mesothelial surface and many extravasated red blood cells in the fibrous layer. × 220. *C*. AFIP Acc. 765838. Organizing hemopericardium. The patient had been struck in the chest by a truck tire he was changing. Organiz-

(Continued on opposite page)

Pericarditis. Occasionally evidence of pericarditis was noted on the surface of the heart at autopsy in the form of loss of luster, with thickening of the epicardium and focal fibrin deposition. Usually hemorrhage was minimal or absent and the pericardial fluid clear, although it sometimes contained flakes of fibrin. Microscopically, the epicardium was thickened with slight fibroblastic proliferation and focal fibrin deposition on the epicardial surface. Leukocytic infiltration, consisting chiefly of lymphocytes and neutrophils, was light and usually focal. When the cardiac injury was associated with lesions of the esophagus or adjacent mediastinal structures, the pericardial cavity sometimes became infected. With purulent pericarditis the surface of the heart was covered with fibrin and vascularized granulation tissue in which many leukocytes, chiefly neutrophils, were present. In some instances, the leukocytic infiltration was more extensive and involved the superficial layers of the myocardium (fig. 1*F*). This condition has been designated traumatic myocarditis by some authors.

Cardiac Hemorrhage or Contusion. The cardiac hemorrhage or contusion was recognized at autopsy as a dark red hemorrhagic area in the wall of the heart. The lesion was observed alone or in association with others, especially lacerations or ruptures. In this series, there were 65 cases of cardiac hemorrhage in which the epicardial and endocardial surfaces were intact, and 64 in which hemorrhage was combined with a laceration or lacerations of one surface or the other. The lesion ranged from a few millimeters to 3 or more centimeters in length; in 12 instances the hemorrhage or contusion was on the right side, in 25 on the left, in 15 on both sides, and in 13 the site was not clearly described. The hemorrhage extended through the thickness of the wall of the heart in some instances, but in many others the location and extent of involvement of the wall made it possible to divide the hemorrhages into 3 groups: subepicardial, myocardial, and subendocardial. In some cases the hemorrhage was minimal and grossly appeared to involve only the subepicardial tissue, usually the region of, or adjacent to, the small surface blood vessels (fig. 1*G*). More extensive hemorrhages, primarily in the myocardium but extending to the subepicardium or endocardium, were grouped as myocardial hemorrhages (fig. 2*A* and *B*). Hemorrhages, limited chiefly to the subendocardial tissue, but sometimes involving the deeper layers of the myocardium or the connective tissue stroma of the valve leaflets, or both, were called subendocardial (fig. 2*F*). Hemorrhage of this type was not observed on gross inspection of the surface of the organ, but only when the heart was opened. Microscopically, the morphologic changes varied with the size, location, and age of the lesion. In lesions of recent origin, they consisted of extravasation of blood, chiefly erythrocytes, into the subepicardial tissue and myocardium, with separation and often disruption of the muscle fibers. In slightly older lesions, the regional blood vessels were dilated and congested, and leukocytes were seen in increased numbers, first in the blood vessels in which they were marginated, then in the hemorrhagic areas and adjacent tissues. With severe hemorrhages, the leukocytic infiltration was prominent and consisted chiefly of neutrophils with a few eosinophils and mononuclear cells. Mast cells were also present in many early but severe hemorrhagic lesions. Pigment-laden macrophages were seen in some

ing hemorrhage on the surface of the parietal pericardium 18 days after trauma. Arrow indicates inner surface of pericardium. × 115. *D.* Same case. Coating of organizing hemorrhage on epicardial surface (indicated by arrow). × 15. *E.* Same case. Focus of fibrin deposition on epicardial surface. × 35. *F.* AFIP Acc. 331525. Epicardial deposition of fibrin with light infiltration of subepicardial tissue and superficial layers of the myocardium. × 35. *G.* AFIP Acc. 294749. Cardiac hemorrhage limited to the epicardial surface. × 12. *H.* AFIP Acc. 278608. Subepicardial hemorrhage with thrombosed surface vessel (*arrow*) associated with epicarditis, laceration of the heart, and mural thrombus formation due to injuries received in helicopter crash (duration 36 hours). × 8½.

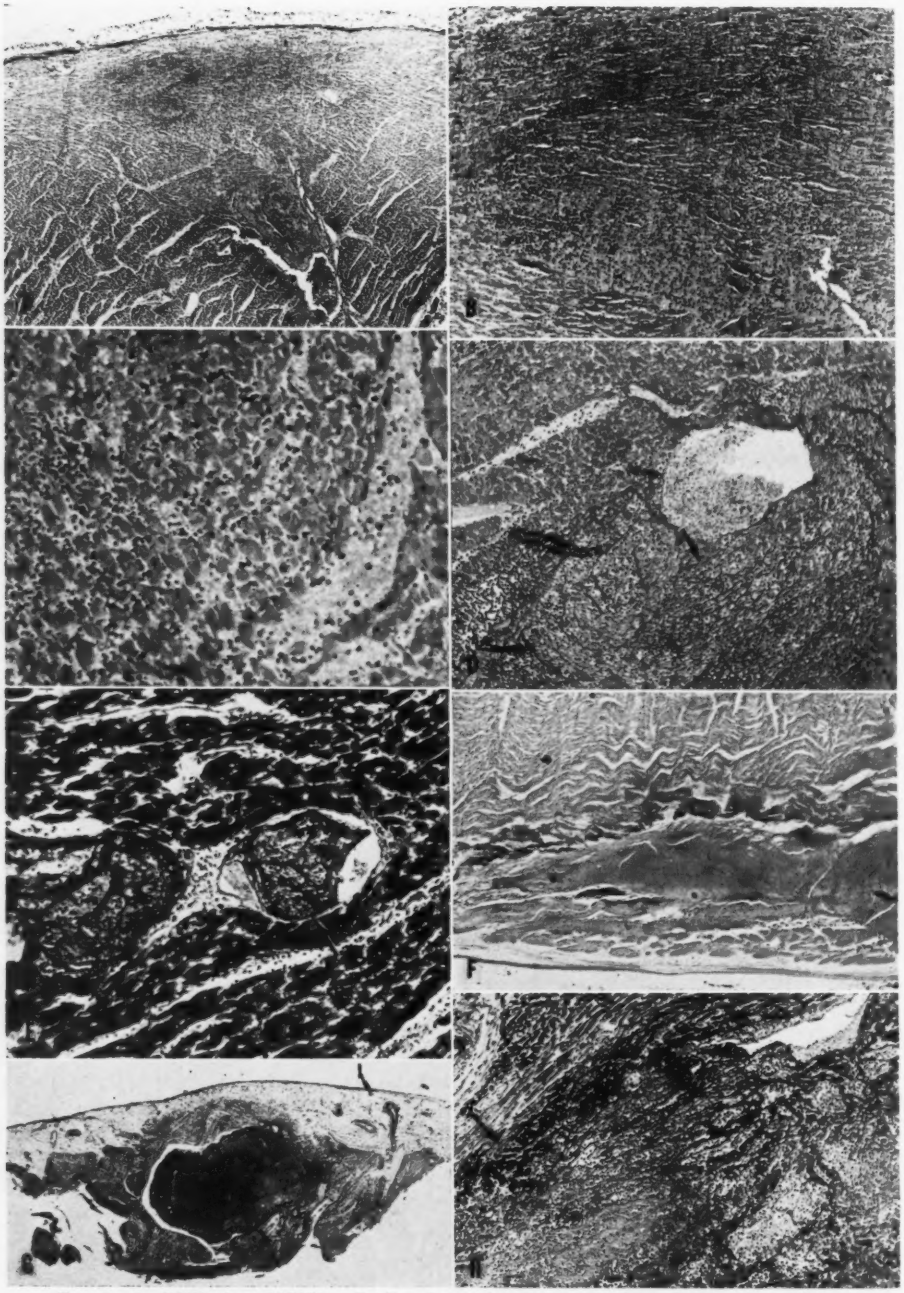

FIG. 2. *A*. AFIP Acc. 335152. Cardiac hemorrhage or contusion of the myocardium as a result of an automobile accident. × 18. *B*. Part of same field at higher power. × 48. Extravasated blood with disruption and separation of the myocardial fibrils. Note the abundance of leukocytes in areas of hemorrhage. *C*. AFIP Acc. 205410. Cardiac hemorrhage with leukocytic infiltration and early necrosis due to contusion of the posterolateral wall of

(Continued on opposite page)

ases with survival of a few hours or more, ut iron stains were negative. Focal necrosis f the muscle, first evident as acidophilia and ss of striations, was a common feature. The ecrotic areas were often limited to a portion f the muscle bundle, a characteristic that istinguishes them from the larger areas of ecrosis in myocardial infarction (fig. 2*C*). ibrin-like strands and masses, some in blood essels, others in the interstitial tissue and etween the muscle fibers, were noted in some ases, in one with a recorded survival time of nly 20 minutes (fig. 2*D* and *E*). With longer urvival, the necrosis became better differentiated and infiltration more intense. Fibroblastic proliferation was seen in the subepicardial fat and hemorrhagic areas. If the hemorrhage reached or involved the endocardium, even in the absence of laceration, another complication occasionally found was mural thrombus formation (fig. 2*G* and *H*). This occurred in both atria and ventricles. In cases of recent origin it appeared as an attached blood clot; in older cases early organization was evident. Definite scarring was not seen in our material.

Lacerations with Contusion. The 64 cases of contusion associated with laceration (but not rupture) were grouped separately. In these cases either of the atria or ventricles might be involved. The lesions were in the right side of the heart in 15 cases, the left side in 24 cases, and both sides in 18 cases. The site was not clearly stated in 7. Lacerations as well as contusions were single or multiple, epicardial, endocardial, or both. Some were superficial, being limited to either the epicardium or endocardium, or deep, involving the myocardium. They ranged in length from a few millimeters to 4 cm. or more. The edges of the lacerations were usually ragged and uneven, although linear lacerations were described. Those of the epicardial surface of the heart involved the surface blood vessels. Hemorrhage along the course of a major branch of a coronary artery was frequently noted. It may be, of course, that ruptures or lacerations of the coronary vessels are overlooked because of associated hemopericardium and gross evidence of laceration. Lacerations of the endocardial surface may occur in either of the atria or ventricles, or both, and involve the papillary muscles, the chordae tendineae, or the valve leaflets or cusps (table 1). Microscopically, the lesions varied according to the extent of the injury and the length of survival. In the immediately fatal lesions or those followed by brief survival, hemorrhage with extravasation of red blood cells that led to disruption and fragmentation of the heart muscle was the chief finding. With lengthening of the survival period to an hour or longer, mural thrombus formation occurred in some instances in which the endocardial surface was lacerated. Leukocytic infiltration, consisting chiefly of neutrophils and a few eosinophils, mast cells, and mononuclear cells, was present in the first few hours. Focal necrosis of muscle was frequent in early lesions, as evidenced by loss of striations and acidophilic staining of the affected fibers. In the older lesions, the leukocytic infiltration was heavier and macrophages were seen in the necrotic areas; sometimes thin strands and masses of fibrin were noted in the smaller blood vessels as well as in the interstitial tissue. Thrombosis of some of the smaller vessels had occurred in an occasional case, but thrombosis of the major coronary arteries or their branches was not encountered in this series (fig. 1*H*).

Rupture of the Heart. Rupture of the heart occurred in 353 cases of this series (table 1), and is perhaps best studied by gross inspec-

left ventricle. × 130. *D.* Same case, another view (× 70) showing an area of myocardial hemorrhage with fibrin strands (automobile accident, survival time 17 hours). *E.* AFIP Acc. 142447. Fibrin thrombi in vascular spaces of myocardium following blast injuries. × 100. *F.* AFIP Acc. 56-19313. Subendocardial hemorrhage as a result of an automobile accident. Hemorrhage in this case was extensive and involved the anterior and posterior walls of the left ventricle. *G.* AFIP Acc. 324481. Contusion of the right ventricle with mural thrombus. × 4½. *H.* Same case. Focal necrosis of muscle at base of thrombus (*arrow*). × 50.

TABLE 2.—*Tabulation of Survival Time and Type of Lesion in the 72 out of 546 Autopsy Cases of Nonpenetrating Trauma to the Heart Whose Injury Was Not Immediately Fatal*

Type and/or Site of Injury	Survival Time							
	30 min.	30 min. 1 hr.	1 hr. 6 hrs.	6 hrs. 24 hrs.	24 hrs. 3 days	3 days 7 days	7 days	Total
Rupture-cardiac								23
Right ventricular			1					1
Right atrium		6	1	2	1			10
Left atrium	1		1		1			3
Interatrial septum		1*	1*		3(1†)(1‡)			5
Interventricular septum					1	1	1	3
Papillary muscle							1	1
Contusion-laceration-cardiac	1	6(1†)	12(1‡)	8	8(1‡)	4	2	41
Laceration/rupture-pericardium			2(1‡)	1	1			4
Hemopericardium		1		1				2
Coronary Rupture			2§					2
Total								72

*Associated with papillary muscle rupture.
†Associated with tricuspid valve rupture.
‡Associated with aortic rupture.
§Associated with cardiac contusion/laceration.

tion at autopsy. The microscopic examination revealed only the changes of acute traumatic rupture.

CARDIAC CONTUSION AND LACERATION

Cardiac contusion and laceration are the commonest lesions of nonpenetrating traumatic heart injury. Cardiac contusion has been reported as occurring *in utero*.[24] Probably because such lesions are so seldom demonstrated at autopsy, traumatic injury has been considered a relatively rare form of heart disease. The current clinical impression regarding injuries of this type has been well expressed in Burchell's[25] couplet:

"And always with a heart contusion
Arise both doubt and much confusion."

In our autopsy material contusion or laceration was the only cardiac lesion in 105 instances (table 1). Thirty-eight of these persons lived for varying lengths of time after injury (table 2). Of the 67 who died as an immediate result of trauma, in only 12 was the primary cause of death considered to be the injury to the heart. Thus, in our series the number whose death was a direct result of cardiac contusion or laceration is relatively small.

Extensive and severe cardiac contusion and laceration from nonpenetrating trauma may occur without external evidence of chest injury;[1, 6, 11] therefore, cardiac injury may not be suspected and the clinical evidence of it difficult to recognize. This is exemplified in the following case.

Case 1 (AFIP Accession 335152). A 20-year-old man, riding a motorcycle, collided with a truck. He was conscious and his blood pressure was 100/70. He had abrasions of the face and lower extremities, but no external evidence of chest injury. Within 30 minutes he became semicomatose, cyanotic, and began to cough. Blood pressure fell to 60/40, and the cardiac rate was 108 per minute. Chest x-ray was considered normal. He was given oxygen therapy and transfused with 500 ml. of whole blood. He died suddenly 6 hours and 45 minutes after injury.

At autopsy the pericardium was intact and distended with 380 ml. of blood. A laceration, 2 by 1.2 cm. and extending 0.5 cm. into the myocardium of the lateral aspect of the left ventricle at its mid portion, was surrounded by ecchymosis (fig. 3 *Left*). A branch of the anterior descending coronary artery was included in the laceration and was responsible for the hemopericardium. In addition, a depressed contused area, 2 by 1.2 cm. in a sagittal plane, was found on the posterior aspect of the left ventricle; when the heart was displaced to the right the depression corresponded to the convexity of the vertebra

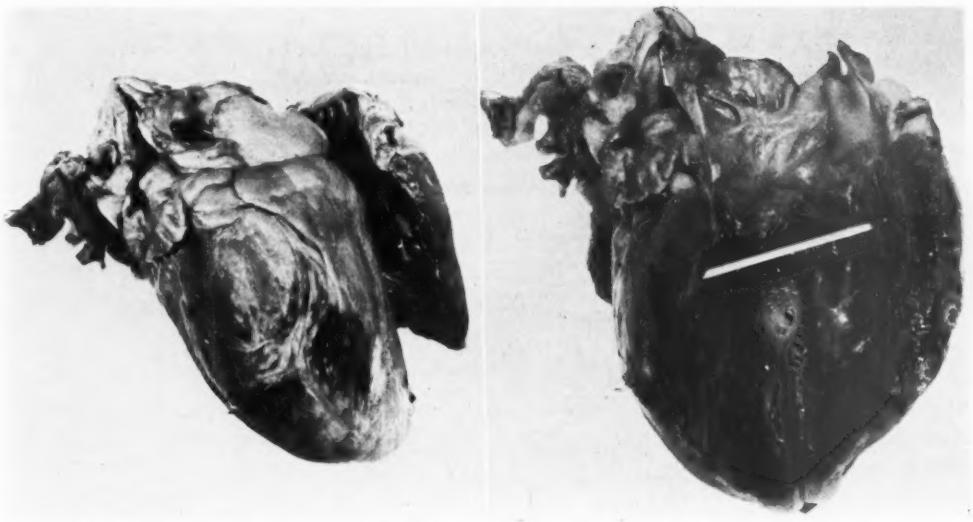

FIG. 3 (Case 1, AFIP Acc. 335152). *Left.* Heart showing area of ecchymosis and contusion of the myocardium in the region of the lacerated branch of the anterior descending left coronary artery. *Right.* Heart opened, revealing laceration of the posterior papillary muscle of the mitral valve (*arrow*) and areas of contusion in the anterior and posterior walls of the left ventricular myocardium.

column. On opening the heart, it was noted that the posterior papillary muscle of the mitral valve was lacerated at its base (fig. 3 *Right*).

Clinically, significant signs or symptoms of cardiac contusion and laceration may be absent or masked by those of injury in other structures. They may also mimic in almost all respects the signs and symptoms of myocardial infarction resulting from coronary artery disease: the character and intensity of the pain, its radiation, and duration. With traumatic injury pain may not be immediate but may follow a latent period of several hours or days[3, 26, 27] and often be more prolonged. Frequently associated chest injury makes it difficult to distinguish the symptoms of cardiac injury.

Occasionally the syndrome of angina pectoris may follow such an injury.[6, 8, 28] Usually the syndrome is transitory because of the rapid healing of the cardiac contusion without significant residual damage. If angina pectoris persists, the probability is that coexistent coronary disease, rather than traumatic injury, is responsible.

Electrocardiographic study may clarify such a clinical picture and, in the relatively asymptomatic case of cardiac contusion, may be the only means of arousing suspicion of cardiac injury. Conduction disturbances, arrhythmias, or QRS abnormalities, as immediate results of trauma, are the more important electrocardiographic indications of injury to the heart.[8] However, electrocardiograms in the majority of cases of suspected cardiac contusion reveal only transitory nonspecific abnormalities of the S-T segment and T wave. Serial electrocardiograms of a typical case are presented in figure 4. Many[7, 21, 27, 29–31] have reported similar or more pronounced electrocardiographic abnormalities in clinical cases of traumatic cardiac injury. However, these electrocardographic findings can hardly be considered justification for an unequivocal diagnosis of myocardial contusion, hemopericardium, or any other specific injury, since they may be produced by a multiplicity of noncardiac causes. This fact has been demonstrated in animals subjected to nonpenetrating cardiac contusion with production of similar electrocardiographic changes, when

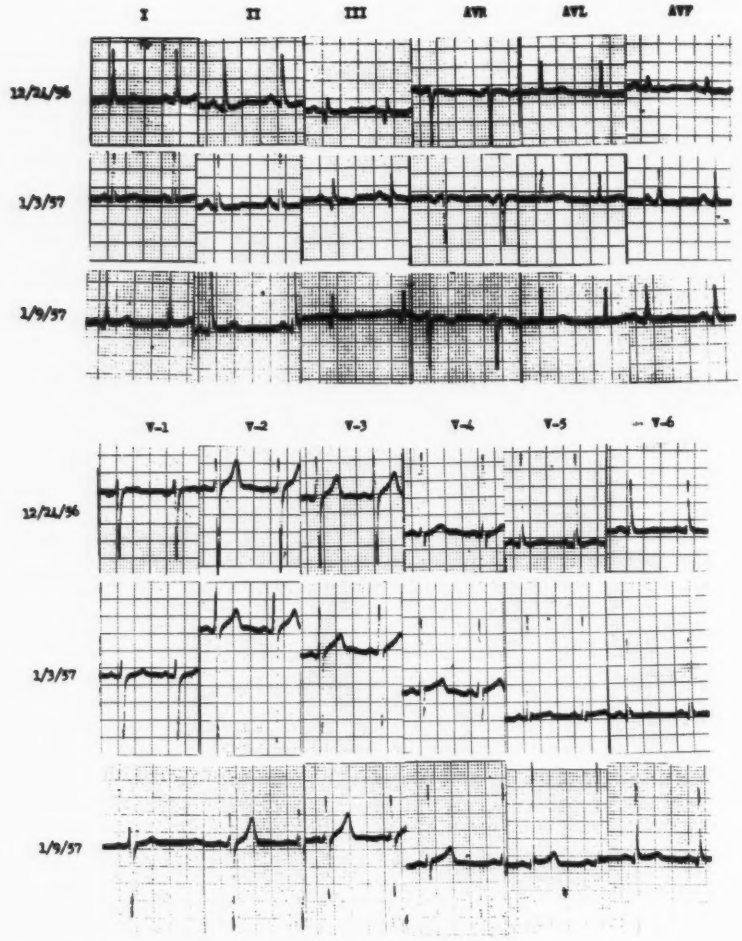

FIG. 4. Serial electrocardiograms obtained on a patient who had sustained nonpenetrating chest injury as a result of an automobile accident. No auscultatory findings or roentgen evidence of cardiac or pericardial injury. Note the nonspecific S-T and T-wave abnormalities present on the day of injury, most evident in leads II, aV_F, V_2, and V_6. Slight progression of these abnormalities developed during the subsequent week. All abnormalities disappeared by the second week after injury.

only mediastinal and pulmonary hemorrhage were demonstrated at necropsy.[23] Thus, this type of electrocardiographic data should not be considered as a conclusive diagnostic criterion of cardiac trauma. Rather, the importance of these nonspecific abnormalities should be to alert one to the possibility of cardiac injury in the traumatized patient, so that careful evaluation may be carried out.

There are a number of late complications of cardiac contusion. Cardiac aneurysm may develop[32, 33] and calcification of the injured myocardium has been reported.[6] More common is rupture of an extensively contused area of myocardium, hours, days, or even weeks after the injury.[3, 34] The second week is considered the most critical,[3] although rupture may be longer delayed if aneurysm ha

rmed.[11, 35] The high incidence of endocardial lesions with formation of mural thrombi favors thromboembolic complications, the cause of death in 2 patients of our series.

Myocardial failure may be either an early or relatively late sequel to myocardial contusion and is sometimes progressive. Extensive traumatic injury to the myocardium in experimental animals has not always caused myocardial failure.[36, 37] As might be expected from these experimental studies, progressive myocardial failure secondary to contusion is relatively rare in man, even though it has been reported.[3, 29, 38] It is indicative of severe and extensive myocardial injury. Early and fatal pulmonary edema, believed to be due to left ventricular failure resulting from severe cardiac contusion, developed in only one patient in our series; but, even in this one, pulmonary contusion was a complicating injury. Before pulmonary edema is attributed to myocardial failure, other possible etiologic factors must be considered, particularly associated pulmonary or cerebral injury. It is controversial whether chronic congestive failure can result from cardiac contusion. This complication was noted only once in our series and was believed to be the result of traumatic myocarditis.

Treatment of Cardiac Contusion

The principles of the management of cardiac contusion have been well presented.[4, 26, 39] Our concepts differ little from those established. Most patients who have suffered cardiac contusion do not require specific treatment, but only immediate restriction of activity and continuous observation. The prognosis is good. Morbidity is slight and recovery usually complete. Bed rest will suffice until the acute cardiac symptoms subside and the danger of the more serious sequelae has passed. Usually this period of rest and observation need be no more than 2 weeks, but, if extensive contusion is suspected, it must be lengthened to 3 or even 4 weeks because of the possibility of delayed myocardial rupture. The precordial pain, which is an almost constant feature, is usually relieved by the milder analgesics, although narcotics may be required. Kissane and Koons,[4] who have had the widest reported clinical experience with cases of this type, are of the opinion that oxygen therapy is almost specific in its ability to relieve the pain and reduce the dyspnea and cyanosis that may be features of the more serious injuries. An accompanying pulmonary injury may account for many of the symptoms in such cases and its response to oxygen is good. Associated thoracic injuries require prompt treatment, for they also produce serious hemodynamic alterations. Should true myocardial failure develop, the prognosis is poor. The accepted therapeutic measures, including digitalization, should be employed. Although thromboembolic complications are a threat to the injured patient, anticoagulant therapy is not indicated because of the danger of hemorrhage in traumatized areas, specifically increasing the threat of serious hemopericardium.

CARDIAC RUPTURE

Cardiac rupture was by far the most common lesion and was encountered in 64 per cent of this autopsy series (table 1). It is also the traumatic cardiac lesion most often reported. In 1935 Bright and Beck[3] collected 152 cases of traumatic cardiac rupture from the literature and analyzed the pathologic features. This has been the largest series reported until now. Our series includes data from 353 cases (table 1), only 2 of which, both instances of interventricular septal rupture, have previously been reported.

The 2 ventricular chambers rupture with about equal frequency. Rupture of the atria is less common, but the right atrium ruptures somewhat more frequently than the left. The trauma that produces rupture may, in some instances, seem disproportionate to the extent of cardiac injury. A blow on the chest by a fist[40] and other minor trauma[41] have been reported to have caused cardiac rupture, and similar observations were made on several cases in our series.

The cause of death in cases of traumatic cardiac rupture is exsanguination or cardiac

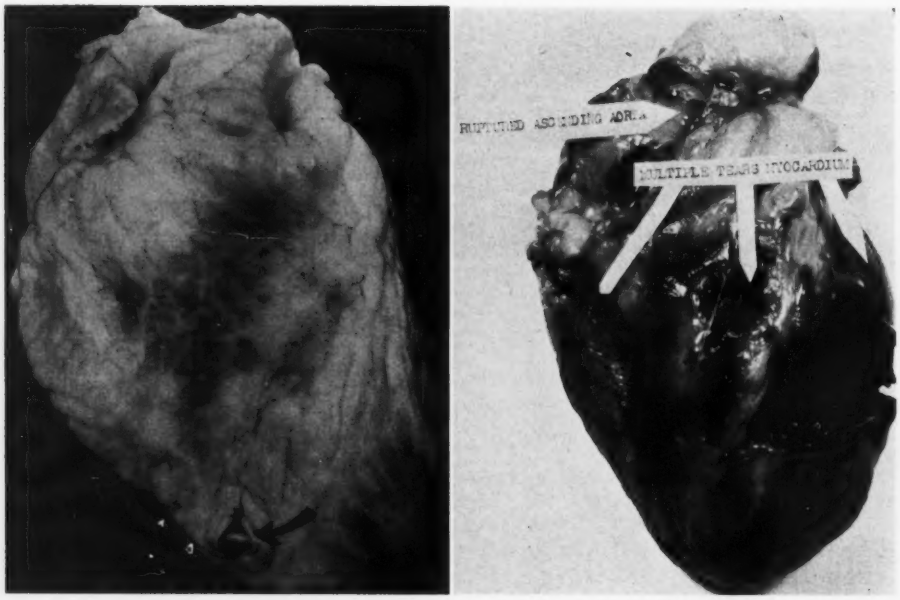

FIG. 5. *Left.* AFIP Acc. 530522. The heart of a 20-year-old man showing a 1.2-cm. rupture of the wall of the right ventricle with minimal abrasions of the anterior epicardial surface occurring as a result of an automobile accident. Chest wall showed only an abrasion of its left posterior aspect. *Right.* AFIP Acc. 281100. The heart of a 27-year-old man showing multiple lacerations with typical complete transection of the ascending aorta. There were, in addition, multiple severe body injuries, the result of an airplane crash.

tamponade, unless other body injury is of sufficient severity to cause death, as it was in more than 50 per cent of the cases of myocardial rupture in our series. The myocardial rupture, either atrial or ventricular, ranged from an extremely small perforation to virtual cardiac destruction (figs. 5 *Left* and *Right*). It was not unusual for external evidence of chest trauma to be minimal or absent.

Survival of an individual who has suffered myocardial rupture is not expected but may occur.[3, 42, 43] Although in our series 13 patients who had atrial rupture survived for a time, only one with ventricular rupture survived even temporarily and in this instance rupture probably was delayed (table 2).

Ventricular Rupture

Traumatic rupture of a ventricle is more common than that of an atrium and rarely permits even temporary survival. One patient in our series lived 4 hours after injury until massive hemorrhage into the thoracic cavity caused death. At autopsy extensive contusion of the right ventricular myocardium with a small rupture suggested that rupture was delayed or that dissection of the necrotic contused area by blood began shortly after injury.

Atrial Rupture

In Bright and Beck's series[3] 14 of 66 with atrial rupture survived temporarily. Recently Kohn et al.[42] reviewed the literature and collected 80 cases of atrial rupture from various causes, 19 traumatic, in which death was not immediate. In our necropsy series there were 67 cases of atrial rupture, excluding those with multiple ruptures; 8 however, had associated aortic rupture (table 1). Thirteen, or 19 per cent, of this group of patients with atrial rupture survived the initial injury. In none of these was the diagnosis made before

death, and in only 1 was the possibility of atrial rupture entertained. The majority died in less than an hour, the range being 30 minutes to 58 hours. Clinical evaluation was understandably limited, but it was found that 6 of the 13 died as a result of hemopericardium with cardiac tamponade, and the others of hemorrhage or other severe bodily injury. Since the surgical repair of cardiac rupture has been reported,[44] recognition of injury of this type has become important for other than academic reasons, since immediate pericardiocentesis and surgical treatment may be lifesaving.

Rupture of Cardiac Septa

Rupture of cardiac septa as a result of nonpenetrating trauma deserves special attention because of the relatively high incidence of survival when it is the major cardiac lesion. In our autopsy series 30 instances of rupture of the interventricular septum and 25 of the interatrial septum were found (table 1), but septal rupture was the sole cardiac lesion in only 5 of the former and 8 of the latter. Brief survival was noted in 5 of the 8 cases of isolated interatrial septal rupture and in 3 of the 5 cases of the interventricular type (table 2). We have also studied clinically 2 additional patients with rupture of the interventricular septum caused by nonpenetrating injury.

No particular area of the interatrial septum seemed more susceptible to rupture, although it frequently extended to involve the border of the foramen ovale (fig. 6). We have not seen a patient that survived traumatic rupture of the interatrial septum for more than 2 days, nor are we familiar with any reported cases. The early diagnostic findings were not specific, and death could not be attributed to the creation of the defect.

Rupture of the interventricular septum was most often associated with rupture of the ventricles (table 1). The most common site of rupture was the muscular portion of the septum; second in frequency was rupture involving both the muscular and membranous

FIG. 6 (AFIP Acc. 268608). Dissection of heart demonstrating a traumatic laceration of the endocardial surface of the interatrial septum 1.5 by 0.8 cm. with a rupture of the septum measuring 0.5 by 0.7 cm. in the area of the foramen ovale. This was one of many severe injuries due to nonpenetrating trauma incurred in a helicopter crash. The patient survived 36 hours.

portions of the septum, and last was rupture of the membranous portion only. Two of the 3 cases of traumatic interventricular septal rupture with temporary survival in our necropsy series have been reported in detail.[45, 46] In 1952, when Pollock et al. reported their cases, they were able to collect 12 of the same type from the literature. Since then at least 7 additional cases[46–52] with survival have been reported; 2[47, 48] we have studied clinically, including catheterization of the right side of the heart. One is unique in that surgical repair of the interventricular defect was done by Pierce[48] as an emergency procedure, with use of hypothermia and cardiotomy. Although

repair was not complete, the size of the defect was reduced so that survival of the patient was possible. Lillihei,[52] however, has successfully repaired such a defect by cardiotomy utilizing a biologic lung oxygenator. Surgical advances, combined with the technics of extracorporeal circulation and asystole, give promise that in the future these defects may be more frequently and thoroughly repaired.

Only severe necrosis and friability of the interventricular septum without an obvious gross defect could be demonstrated in a 3-year-old girl in our autopsy series, although the clinical and pathologic impression was that a left-to-right shunt had developed through this area. Initially a cardiac murmur was not heard, but by the second day after injury a grade IV systolic murmur became audible over the entire precordium and was associated with a systolic thrill. The electrocardiogram (fig. 7 *Top*) demonstrated right bundle-branch block. Death occurred suddenly on the third day, presumably the result of arrhythmia. This case demonstrated a probable frequent evolution of a traumatic interventricular septal defect from contusion to necrosis and consequent sloughing of the septal area involved.

Fatal arrhythmia or conduction disturbance may result from the creation of a traumatic interventricular septal defect; however, survival of the patient with such a lesion depends primarily upon the size of the defect and the hemodynamic consequences. The pulmonary vascular resistance that develops secondary to these hemodynamic alterations influences the course. A small defect will produce little alteration and the patient would be expected to survive. A large defect resulting in a left-to-right shunt of major magnitude may produce pulmonary edema and death relatively quickly. On the other hand, as in Pollock's case,[45] enough pulmonary vascular resistance may develop to prolong the course with the production of pulmonary hypertension and eventual right ventricular hypertrophy, failure, and death.

The characteristic clinical manifestations of traumatic interventricular septal rupture may be evident immediately after injury, but that they often are delayed suggests that contusion of the septum may be the initial injury, followed by necrosis and finally rupture. The clinical findings are much like those in patients with a defect of the congenital type, but the electrocardiographic abnormalities are usually more pronounced and often demonstrate conduction disturbances, particularly bundle-branch block (fig. 7). Atrioventricular block has also been noted.[49]

Coronary Artery Injury

The relation of nonpenetrating traumatic injury to the production of coronary artery lesions, particularly coronary thrombosis, has been a controversial subject. Warburg[8] and Boas[28] are proponents of the belief that nonpenetrating trauma may produce coronary thrombosis and that this sequence is more frequent than generally appreciated. Others[5-29, 53] are of the opinion that coronary thrombosis may occur but is rare except in cases of pre-existent coronary disease. We are in agreement with the latter view. In neither our clinical experience nor our autopsy material have we been able to establish the presence of thrombosis, due entirely to nonpenetrating trauma, in a major artery. On the contrary, 2 individuals in our series, one who lived 33 and the other 17 hours after injury, were found to have severe myocardial contusion of the area traversed by the anterior descending coronary artery. Extensive hemorrhage surrounded the artery along most of its course, but coronary thrombosis had not occurred. The demonstration that coronary thrombosis did not result even when there was evidence of severe traumatic injury along the course of the artery favors our impression that thrombosis of a major coronary artery as a result of nonpenerating trauma is unusual.

On the other hand coronary artery injury in the form of laceration or rupture is not rare. Complete rupture of a major coronary artery was observed in 9 cases and an intimal laceration in a tenth case of our series. In the presence of cardiac maceration, coronary rupture was common, but these cases are not included in this tabulation. Of the 10 individuals, 8 died as an immediate consequen-

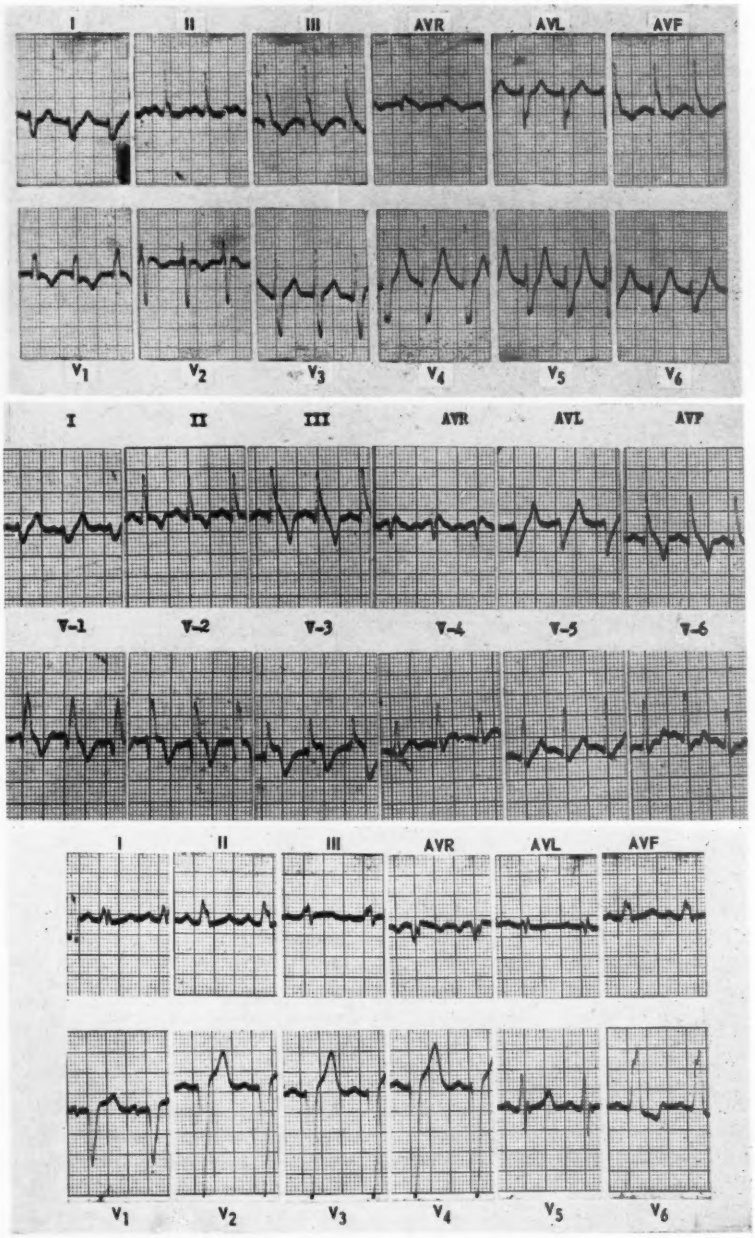

FIG. 7. *Top.* AFIP Acc. 729015. Electrocardiogram demonstrating right bundle-branch block as a result of interventricular septal necrosis due to nonpenetrating trauma. *Middle.* AFIP Acc. 481399. Electrocardiogram demonstrating right bundle-branch block and suggesting anteroseptal necrosis in a patient with an interventricular septal defect due to nonpenetrating chest trauma. *Bottom.* WRAH Reg. No. 3774003. Electrocardiogram demonstrating left bundle-branch block in a 27-year-old man who developed a traumatic interventricular septal defect as a result of nonpenetrating chest injury incurred in an automobile accident.

FIG. 8. Case 2. Postero-anterior and left lateral chest roentgenogram taken 4 months after injury, demonstrating some straightening of the left cardiac border but no definite abnormality.

of the injury: 6 with myocardial rupture, 1 with aortic rupture, and the eighth with contusion of the right ventricle. The 2 others lived for 2 hours and 6 hours, respectively. Both sustained rupture of the anterior descending branch of the left coronary artery at the site of severe contusion. In neither was myocardial infarction demonstrated. Both had marked hemopericardium and cardiac tamponade. These, rather than myocardial infarction, are the important sequelae of laceration of a coronary artery. Case 1 summarized the clinical and pathologic data from one of these patients.

VALVULAR LESIONS

The occurrence of valvular lesions as a result of nonpenetrating trauma has been well known for many years. Most reports have been concerned with traumatic rupture of the aortic valve,[49, 54] and until recently[49] surgical treatment was not considered feasible. Less frequently other valvular lesions have been attributed to nonpenetrating trauma, including 4 instances[55-57] of mitral stenosis and 1 of mitral insufficiency.[58] However, it is questionable that the etiologic relationship of trauma was established in these particular instances. Severe hemorrhage into a valve or adjacent area was found occasionally in our autopsy series and might conceivably have produced similar lesions if the individual had survived associated extensive endocardial laceration or myocardial rupture. The one instance of valvular rupture without associated cardiac injury was in a congenitally bicuspid aortic valve. It is of interest that of the 4 cases of aortic valve rupture in this series, 2 were of congenitally bicuspid valves. The atrioventricular valves were most frequently involved (table 1) but usually myocardial rupture was also present. Probably it is for this reason that traumatic rupture of an aortic valve is more commonly seen clinically. Only one individual in our series survived valvular rupture, and he lived 25 hours after complete separation of the anterior leaflet of the tricuspid valve. This lesion was only one of a number of severe endocardial lacerations in addition to a traumatic interatrial septal defect.

INJURIES OF PAPILLARY MUSCLES OR CHORDAE TENDINEAE

Traumatic lesions of the papillary muscles include contusion, laceration, and rupture.

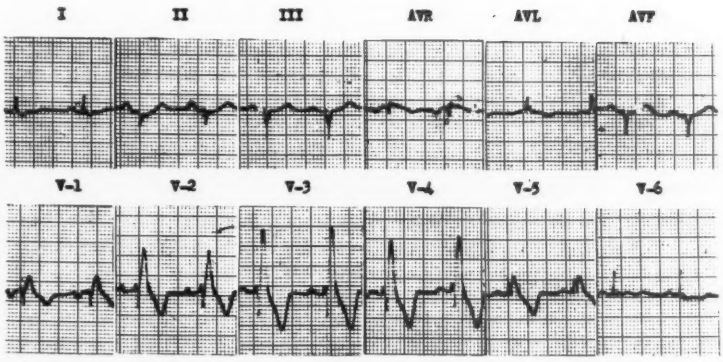

FIG. 9. Case 2. Electrocardiogram demonstrating right bundle-branch block.

Involvement of chordae tendineae is almost exclusively that of rupture.

Rupture of the papillary muscles was encountered 24 times in our autopsy series and in all but one instance myocardial lesions, frequently myocardial rupture (table 1), were associated. Laceration or contusion of a papillary muscle, as demonstrated in case 1, was somewhat more frequent. No one particular papillary muscle appeared to be predisposed to injury. Three patients with rupture of a papillary muscle survived. Two of these lived 45 minutes to an hour and in both there was an associated traumatic interatrial septal defect. In one a papillary muscle of both the mitral and tricuspid valves had ruptured. The third case is sufficiently unique to warrant a detailed report.

*Case 2.** This 28-year-old man was involved in an automobile accident and hospitalized 2 hours after injury. He was in shock. A chest roentgenogram revealed rib fractures and a probable left hemothorax. On left thoracentesis, 1,900 ml. of blood were recovered. Supportive treatment included transfusions of whole blood. Four days after injury a systolic murmur was first heard at the cardiac apex along with a pericardial friction rub. The patient responded to treatment. Four months later his only symptoms were moderate exertional dyspnea and fatigue. Examination at this time revealed a grade II systolic murmur along the left sternal border and a pulsating liver. Venous pressure was 132 mm. of water. The chest roentgenogram (fig. 8) was normal. The electrocardiogram (fig. 9) demonstrated right bundle-branch block. Right heart catheterization study performed at Brooke Army Hospital revealed no evidence of shunt and normal right ventricular and pulmonary artery pressures.

Ventricularization of the right atrial pressure was the important finding (fig. 10). Tricuspid insufficiency due to traumatic rupture of a papillary muscle or tricuspid valve was considered the most probable diagnosis. Surgical correction was believed to be feasible and was performed by D. A. Cooley, M.D., assisted by T. H. Hewlitt, Lt. Col., MC, using technics of extracorporeal circulation. On cardiotomy it was found that the anterior papillary muscle was ruptured and partially regurgitated into the right atrium with each systole. Good repair of the ruptured papillary muscle was accomplished. An incidental finding was rupture of the pericardium. The immediate postoperative course was good, but massive hemorrhage occurred within 12 hours, apparently from the right atrial appendage, and the patient died.

The prognosis of patients with rupture of a papillary muscle has been considered grave, with death expected in a matter of hours or days after injury. This is not always the course. Rupture of a papillary muscle in the left side of the heart with its relatively high pressure would not be as well tolerated as rupture of one of the tricuspid papillary muscles in the low pressure side of the heart.

The clinical features thus depend upon the papillary muscle involved. If in the mitral valve, the findings of sudden severe mitral insufficiency with rapidly developing pulmonary edema may predominate. The signs and symptoms of tricuspid insufficiency that follow rupture of a papillary muscle of that valve may be less dramatic and, as in the re-

*The clinical data on this case were supplied through the courtesy of Weldon Walker, Col., MC, previously Chief of Cardiology, Brooke Army Hospital.

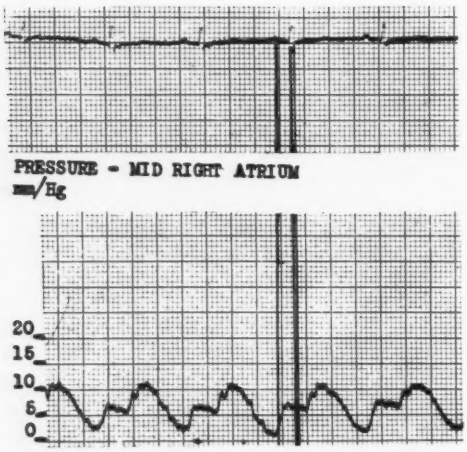

FIG. 10. Case 2. Right atrial pressure curves typical of tricuspid regurgitation obtained during right heart catheterization.

ported case, minimal. The murmurs that may result from rupture of a papillary muscle vary widely and have been reported[59] as systolic, diastolic, or both. In 2 cases of traumatic rupture of papillary muscles, proved at autopsy,[10, 60] no murmurs were heard; neither were any recorded in 2 similar cases of our series, and in a third only a grade II systolic murmur of tricuspid insufficiency was heard.

The clinical findings in cases of rupture of the chordae tendineae depend upon the number ruptured and the valvular insufficiency produced. Significant hemodynamic alterations may be absent, and a murmur may be the only finding. The murmur, as in papillary muscle rupture, may vary in character[61, 62] and be inconstant.[63] In one case[63] it has been described as resembling the sound of a jew's harp. If significant insufficiency of the tricuspid or mitral valve results, the hemodynamic consequences and the clinical picture would be identical to those of rupture of a papillary muscle.

ARRHYTHMIAS AND CONDUCTION DEFECTS

One of the more common consequences of myocardial injury is the production of arrhythmias, particularly those of supraventricular origin. Sinus tachycardia often accompanies cardiac injuries caused by trauma but cannot be attributed to the cardiac injury alone. Sinus bradycardia as a result of trauma is reportedly rare. Atrial fibrillation or flutter is probably the most common arrhythmia produced. Traumatic injury may also cause premature ventricular contractions as well as the more serious ventricular arrhythmias. The production of ventricular tachycardia or ventricular fibrillation is undoubtedly the mechanism of death in some instances of cardiac contusion. There is no definite correlation between the extent of myocardial injury and the production of arrhythmias, since a normal sinus rhythm may persist or only sinus tachycardia be produced in the presence of extensive cardiac contusion, while fatal ventricular arrhythmias may result from an apparently minor injury.

In case of proved or suspected cardiac injury in which premature ventricular contractions develop, especially if from more than one focus, prophylactic therapy such as quinidine is indicated. The therapy of ventricular tachycardia is the same as that of arrythmias caused by other cardiac diseases.

The supraventricular arrhythmias, atrial fibrillation being the most common, likewise are treated much as in other diseases. Since those of traumatic etiology are paroxysmal, frequently transient, and rarely if ever persist in the absence of other heart disease, the immediate goal should be conversion to normal sinus rhythm. The following case demonstrates the occurrence of supraventricular arrhythmias complicating marked hemopericardium and probable severe myocardial contusion.

Case 3 (WRAH Reg. No. 2835015). This 45-year-old man was involved in an automobile accident in which he was thrown against the steering wheel. Examination revealed severe contusions of the anterior chest wall, multiple fractures of the ribs, and a fracture of the sternum that produced a flail chest. X-rays demonstrated a tension pneumothorax. Therapy included thoracotomy with drainage of the left pleural cavity and application of towel clips to the thoracic wall as a means of support. Tracheotomy was performed. The patient was transferred to Walter Reed Army Hospital 2 days after the accident.

On admission sinus tachycardia with a rate of 110 per minute was noted, blood pressure was 130/90, and there were distant heart sounds and a pericardial friction rub. The features of an x-ray of the chest were compatible with hemopericardium, mediastinal hemorrhage, and pleural effusion (fig. 11). Soon after admission atrial fibrillation (fig. 12 *Top*) ensued and was treated with Digoxin. During the next 7 days the atrial arrhythmias of fibrillation and flutter (fig. 12 *Middle*) appeared intermittently with sinus rhythm (fig. 12 *Bottom*). Twelve days after injury signs of cardiac tamponade due to hemopericardium developed and pericardial drainage was carried out through a partial pericardiectomy. Atrial fibrillation recurred in the immediate postoperative course but was soon converted to a normal sinus rhythm, which was maintained thereafter.

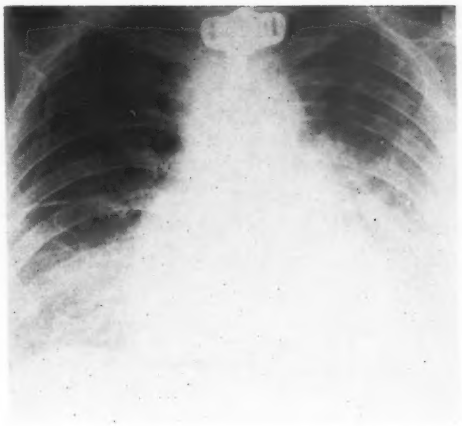

FIG. 11. Case 3. Chest roentgenogram taken shortly after injury, interpreted as demonstrating mediastinal hemorrhage, hemopericardium, and bilateral pleural effusion, probably hemothorax. Tracheotomy tube in place.

Conduction disturbances and intraventricular and atrioventricular conduction defects[8] also complicate traumatic cardiac injury. The intraventricular conduction defect may be transient[64] or permanent. Right or left bundle-branch block may occur (fig. 7), particularly if the contusion or the rupture involves the interventricular septum. Traumatic myocardial injury may result in varying degrees of A-V block, from prolonged P-R interval to complete block. In some cases this may be a transient phenomenon,[65] in others, permanent.[66] As in other cases of A-V block, a Stokes-Adams syndrome may occur. In our series only one instance of A-V block as the result of trauma was recorded and in this case it was manifested only by a prolonged P-R interval.

PERICARDIAL INJURY

The pericardium is frequently involved in nonpenetrating traumatic injuries of the heart and pericardial laceration, rupture, or hemopericardium may often be an isolated lesion (table 1).

Although rupture of the heart without associated pericardial rupture has been considered rare,[67] in our series it was found in 71 of the 161 cases of isolated atrial or ventricular rupture, but in only 11 in which there were multiple ruptures. Cardiac contusion or laceration frequently occurred without a pericardial lesion. Individuals subjected to apparently the same trauma would, in one instance, show extensive pericardial rupture and, in another, no evidence of injury.

If pericardial laceration or rupture is an isolated lesion, it is usually of no consequence unless complicated by hemorrhage from a lacerated pericardiophrenic artery.[68] Herniation of the heart through the ruptured pericardium usually causes no difficulty but may result in strangulation and sudden death.[26] Herniation without apparent ill effect occurred in 3 patients of this series. Pericardial laceration and rupture undoubtedly are more frequent in traumatized individuals than realized and may be easily overlooked or clinically suggest pericarditis.

A serofibrinous or purulent pericarditis may be a sequel of nonpenetrating trauma. Purulent pericarditis is rare and usually the result of combined lesions, including pericardial laceration and associated lesions of the esophagus or respiratory structures. Pneumopericardium occurring under similar circumstances is usually a benign complication,[8] requiring no specific treatment. Mediastinitis and mediastinal emphysema may complicate the clinical picture.

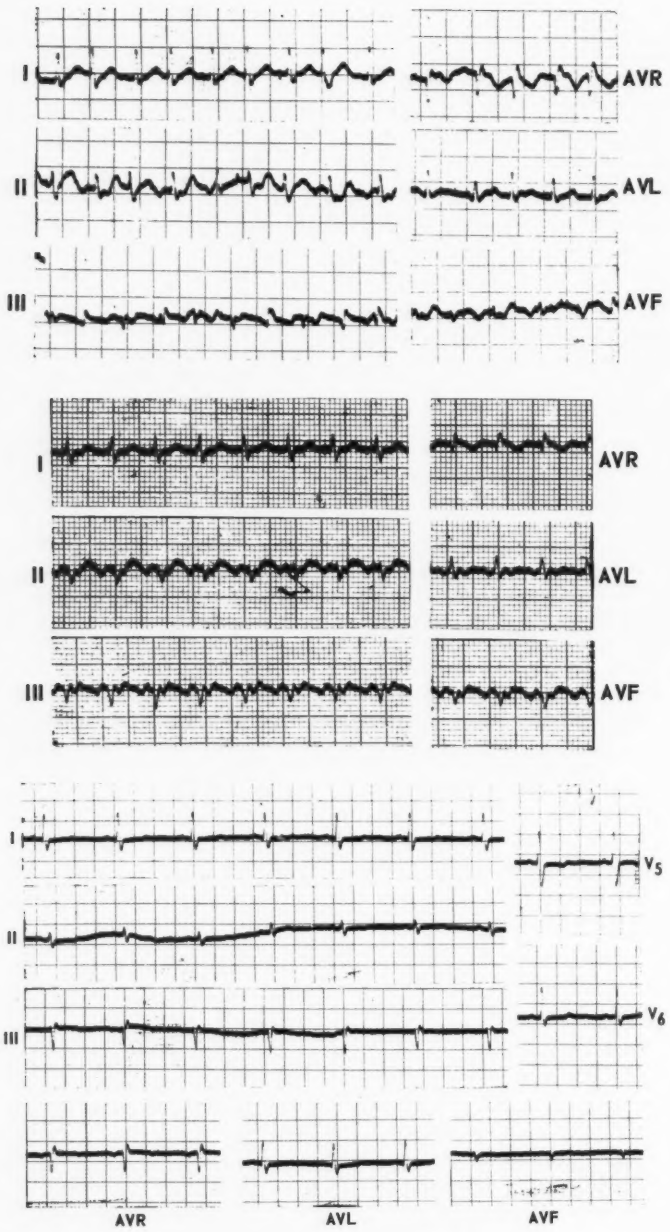

FIG. 12. Case 3. Serial electrocardiograms recorded during the first week after injury demonstrating: *Top.* atrial fibrillation, *Middle.* atrial flutter, and *Bottom.* normal sinus rhythm. Nonspecific ST-T wave changes compatible with pericardial injury and digitalis effect.

Hemopericardium is common and in a mild form often accompanies epicardial hemorrhage or other minor myocardial injury. In many instances it is the cause of transient changes in the S-T segment and T waves seen in the electrocardiogram. Usually it resolves rapidly. Diagnostic pericardiocentesis is not needed and medical observation to insure against development of increasing hemopericardium and possible cardiac tamponade is the only requirement.

If evidence of cardiac tamponade appears, pericardiocentesis should be performed without delay. If the hemopericardium has progressed rapidly, the possibilities of laceration of one of the coronary vessels, severe myocardial laceration, or atrial rupture must be considered. If pericardiocentesis fails because of clots, or if hemopericardium rapidly recurs, surgical treatment is indicated to locate and control the site of bleeding if possible.

In cases in which hemopericardium shows evidence of progression, but not of such a degree as to produce signs of cardiac tamponade, it is problematical whether immediate pericardiocentesis is indicated. Hemopericardium may be accompanied by a serous pericardial effusion and, if left undisturbed, will often regress. If hemopericardium appears to be moderate in amount and shows no inclination to regress, pericardiocentesis is indicated. It is because of the possibility of the development of constrictive pericarditis[8, 69] that hemopericardium of this degree is best evacuated. In our autopsy series we had no proved instance of constrictive pericarditis nor have we seen this complication in any of our clinical cases. However, in one case of fatal left ventricular rupture incurred in an automobile accident, the pericardium was 1.5 cm. thick, apparently as the result of organization of hemopericardium suffered in an automobile accident 6 months previously.

Hemopericardium with pericardial effusion may develop so insidiously during the first few weeks after trauma that it may go unnoticed at early examinations. For this reason careful cardiovascular evaluation of the traumatized patient should continue for at least 2 weeks after injury. The following case demonstrates the massive proportions hemopericardium may reach following trauma, if repeated evaluations for possible cardiac injury are neglected and attention is focused on the more obvious injuries.

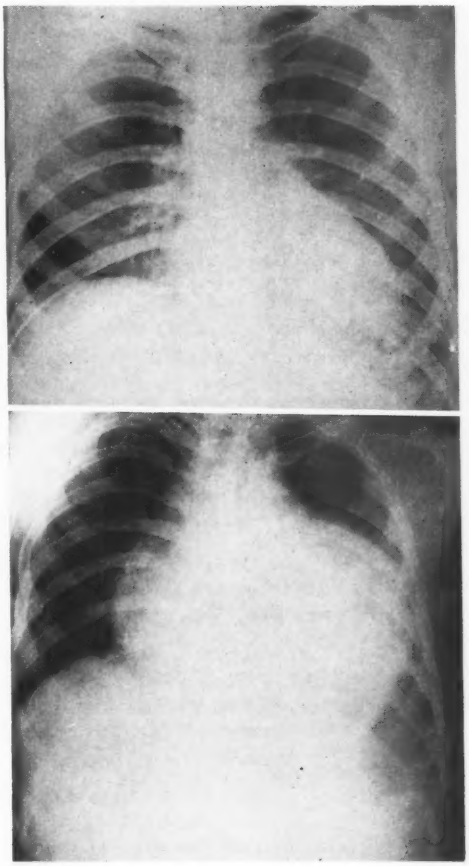

FIG. 13. Case 4. WRAH Reg. No. 85295. *Top.* Chest roentgenogram obtained soon after injury, showing right clavicular fracture, but no definite evidence of hemopericardium. *Bottom.* Repeat roentgenogram 1 month after injury demonstrating massive hemopericardium.

Case 4 (WRAH Reg. No. 85295). This 23-year-old man was a front-seat passenger in an automobile struck by a trailer truck. When admitted to the hospital he was unconscious, with scalp and face lacerations and a fracture of the right clavicle. Blood pressure was 150/76. Babinski reflexes were positive bilaterally, and

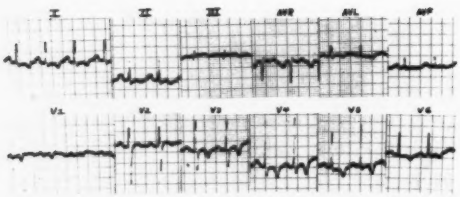

FIG. 14. Case 4. WRAH Reg. No. 85295 Electrocardiogram (1 month after injury) demonstrating S-T segment and T-wave abnormalities compatible with pericarditis. P-R interval measures 0.22 second.

spastic paraplegia and paresis of the right arm were present. A chest roentgenogram (fig. 13 *Top*) revealed the clavicular fracture but no significant abnormality of the cardiac silhouette. The patient remained in coma and his temperature was elevated. Treatment was supportive and included the administration of antibiotics. Chest roentgenogram taken a week after injury was apparently unchanged from the first. Hemograms showed that the hemoglobin had fallen from 13.5 Gm. per 100 ml. 10 days after the accident to 8.5 Gm. 2 weeks later, despite transfusions of whole blood totaling 1,500 ml. given during the interval. The site of bleeding was not found. Three weeks after injury bilateral temporal decompression was carried out because of persisting coma, but hematoma was not demonstrated. A chest roentgenogram taken 1 month after injury revealed marked enlargement of the cardiac silhouette (fig. 13, *Bottom*) believed to be due to pericardial effusion or hemopericardium. An electrocardiogram (fig. 14) demonstrated S-T and T-wave abnormalities compatible with pericarditis or myocardial injury, and a P-R interval of 0.21 to 0.22 second. Signs of cardiac tamponade or congestive failure were absent. The area of precordial dullness was increased and heart sounds were distant, but there was no pericardial friction rub. Pericardiocentesis was performed and 600 ml. of serosanguineous fluid were removed. The remaining hemoseropericardium regressed without further treatment. Studies for tuberculosis were negative.

MEDICOLEGAL CONSIDERATIONS

Traumatic heart disease has become an important medicolegal problem as emphasized by the many articles in the literature.[7, 28, 70, 71] Aside from strictly medical considerations concerning nonpenetrating traumatic cardiac injury, the legal implications of the injury in our present-day society require evaluation. Excellent criteria[72, 73] have been established whereby the relation of trauma to production of cardiac disability may be gauged.

In the over-all management of a patient with either supposed or actual traumatic cardiac injury, the psychologic implications are of primary importance.[4] Permanent or serious disability as a result of traumatic cardiac lesions has been demonstrated to be rare and an optimistic approach to the patient's injury is justified until there is definite evidence to the contrary. Every measure to prevent neurosis should be taken, for many individuals are susceptible to iatrogenic disease whether or not they are conscious of the possibility of a disability claim. Litigation too frequently stems from undue concern on the part of the physician or a thoughtless comment in respect to unproved or minor traumatic injury to the heart.

The factor of pre-existent cardiac disease is one that cannot be evaluated accurately in many cases of traumatic injury, and yet it is often the most important.[5, 74] There are reports demonstrating that pre-existent disease was responsible for cardiac disability erroneously attributed to an incidental traumatic injury.[75] It has also been shown that a diseased heart is more susceptible to traumatic injury than a normal heart.[16, 76] Thus trauma may produce cardiac disability that would not have appeared for some time in the natural course of the disease. The problem of aggravation of pre-existent disease by trauma is most difficult in the medicolegal evaluation of traumatized patients.

No answer to this medicolegal dilemma can be given. However, an appreciation of the natural course of the cardiac lesions that may be produced by trauma and a knowledge of the criteria established for substantiating a relation between injury and cardiac disability will enable the physician to evaluate the majority of cases properly. It must be recognized, however, that the role of trauma in the etiology of the cardiac disability cannot be established with certainty in some cases of pre-existent heart disease.

Summary and Conclusions

1. Cardiac injury caused by nonpenetrating trauma is common, but often the lesion is minimal and the morbidity slight. The mortality rate from injuries of this type is low, and when death occurs, it is most often the result of cardiac rupture.

2. The character of forces responsible for the production of these injuries may be grouped in seven categories: direct, indirect, compressive, decelerative, blast, concussive, and combined forces.

3. Our evaluation of 546 autopsy cases and additional clinical patients with nonpenetrating traumatic cardiac injury has shown that myocardial rupture is the most common finding at autopsy, whereas myocardial contusion and pericardial lesions are the most common injuries encountered clinically.

4. Almost invariably ventricular rupture is immediately fatal, but survival after atrial rupture has been shown to be possible, and since it is amenable to surgical treatment, prompt diagnosis is essential. An individual may also survive rupture of one of the cardiac septa, particularly the interventricular septum. This lesion may now be considered surgically correctible.

5. Although myocardial contusions or traumatic pericardial lesions are often well tolerated, the sequelae may be serious. Therefore, careful clinical evaluation of every traumatized individual for possible cardiac injury is imperative so that the more serious complications may be recognized and treated promptly.

6. Thrombosis of a major coronary artery as a result of nonpenetrating trauma was not observed in this series and is considered rare.

7. The effect of nonpenetrating trauma on a previously diseased heart is often serious. The extent to which trauma aggravates a preexistent cardiac disease is often hard to assess.

Acknowledgment

The authors wish to acknowledge the assistance of Mrs. Helen Knight Steward in the most helpful editing of this series of articles on traumatic heart disease.

Summario in Interlingua

1. Lesiones cardiac per trauma non-penetrante es commun, sed frequentemente illo es minime e le morbiditate es leve. Le mortalitate es basse, e le mortes que occurre es le plus frequentemente le resultato de ruptura cardiac.

2. Le fortias responsabile pro tal lesiones pote esser gruppate in septe categorias: Directe, indirecte, compressive, decelerative, explosional, concussive, e combinate.

3. Nostre evaluation de 546 necropsias e datos clinic additional ab patientes con nonpenetrante lesiones cardiac ha monstrate que ruptura myocardial es le constatation le plus commun al necropsia, durante que contusion myocardial e lesiones pedicardial es le constatationes le plus commun in le examine clinic.

4. Ruptura ventricular es quasi invariabilemente sequite per morte immediate, sed il ha essite demonstrate que superviventia post ruptura atrial es possibile. Proque ruptura atrial es attaccabile per mesuras chirurgic, un prompte diagnose es indispensabile. Il es etiam possibile superviver a ruptura de un del septos cardiac, specialmente del septo interventricular. Il es permissibile al tempore presente considerar iste ultime typo de lesion como chirurgicamente corrigibile.

5. Ben que contusiones myocardial o traumatic lesiones pericardial se tolera frequentemente satis ben, le sequellas pote esser grave. Ergo, un meticulose evaluation clinic de omne victima de trauma pro le presentia possibile de lesiones cardiac es indicate a fin que le plus grave complicationes pote esser recognoscite e tractate promtemente.

6. Thrombose de un major arteria coronari como resultato de trauma non-penetrante esseva absente in le presente serie e pote esser considerate como rar.

7. Le effecto de trauma non-penetrante in cordes anteriormente morbide es frequentemente multo serie. Le grado a que trauma resulta in un aggravation de pre-existente morbo cardiac es frequentemente difficile a estimar.

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"Pulseless Disease"—Description by Robert Adams, 1827

An Historical Note

JAMES H. CURRENS, M.D.

In reading some of the literature on Cheyne-Stokes breathing in the Dublin Hospital Reports, I have come upon an account by Robert Adams of an early description of "pulseless disease." This happens to be in the same report that contains the classical description of Robert Adams of the Adams-Stokes syndrome in 1827. It is probable from the case report that the patient suffered a dissecting aneurysm of the aorta to account for the pulseless state rather than being due to the "Complete Ossification of the Coronary Arteries of the Heart and of the Aortic Valves," which was Adams' interpretation of the case. An autopsy was done, but the examination of the aorta was not described.

"A gentleman, aetat. 68, of a pallid countenance, yet full and corpulent, while exerting himself in arranging some books on a high shelf in a library, suddenly felt severe pain in his chest, extending down his right arm, accompanied by a sensation of numbness: his sight became dim, he had vertigo, but did not fall. From that moment his breathing became oppressed, and in a little time he discovered that his pulse, which was unaccountably weak in his left arm, was altogether imperceptible in the right.

"On the following day, the 18th of October, he had still further grounds for alarm; the most careful examination could not detect the least pulsation in any artery in the body; nor was the movement of the heart sensible to the hand laid over the breast; an obscure undulating motion could alone be heard when the ear was for some moments attentively applied to the side of the thorax.

"His breathing was high and laborious, and could only be performed when the body was nearly erect, inclined a little backward or forward. At night he became worse, and enjoyed no sleep; he occasionally turned on his side with a wish to rest, but this posture increased the dyspnoae, and could be preserved only for a few moments.

"Although this gentleman was perfectly aware of the alarming nature of his symptoms, being himself a physician, he was cheerful, and his countenance was but little disturbed. His appetite was not good; but he was able to eat some chicken or fish for his dinner daily. His digestive organs performed their functions but imperfectly; he suffered great distress from flatulence; thus he remained for six weeks, with little alteration in his symptoms, except that his strength was observed declining daily and his breathing becoming more difficult; his rest during the night was still more imperfect; during the entire of this distressing period, *no pulse was to be felt in any artery in the body.* Although I daily made the most careful examination, it was in vain."—ROBERT ADAMS. *Cases of Disease of the Heart, Accompanied with Pathological Observations.* The Dublin Hospital Reports and Communications in Medicine and Surgery **4**: 443, 1827.

Plasma-Clearing Effect of Gastric Mucin in Healthy and Atherosclerotic Subjects under Basal Conditions

By Baldo Rossi, M.D., and Vincenzo Rulli, M.D.

Other substances, in addition to the heparin clearing factor, exert a plasma-clearing effect under experimental conditions. A mucin compound extracted from the pig gastric mucosa has recently been included among such substances. Its clearing effect, as evaluated by variations in plasma optical density, is as constant and evident as that of heparin, both in normal and atherosclerotic subjects under basal conditions. The resemblance in function between gastric mucin and heparin is accompanied by similarities in molecular structure between the 2 compounds. Gastric mucin may belong among the factors that under physiologic conditions regulate the transport and some phases of the intermediary metabolism of lipids.

THE optical density of the plasma is related to the physicochemical state of the colloidal macromolecules and depends especially upon the concentration of the large lipoprotein aggregates (chylomicrons). Both in normal and atherosclerotic subjects the basal optical density shows great variability in different individuals and at different times in the same individual, and cannot therefore be used as a discriminating feature.[1] Within certain limits of time, however, it remains fairly constant under basal conditions, so that by following its variations in the course of short experiments it is possible to assess the clearing effect produced by heparin and other substances. Gastric mucins, and especially an acid aminopolysaccharide isolated from hog gastric mucins, has recently been included among the substances having a clearing effect. Such mucins, when administered orally to rabbits, produce a diminution of plasma lipids and enhance, to a small but significant degree, the in vitro plasma-clearing power on lipid substrates.[2, 3] The last-mentioned phenomenon has been demonstrated also in human beings.[4]

We report in the present paper variations in plasma optical density observed in a group of healthy subjects and another group of atherosclerotic patients after oral administration of gastric mucin.

From the Centro per la Lotta contro il Reumatismo e Cardiopatie di Roma (V. Puddu, M.D., Director), Ospedale Policlinico, Rome, Italy.

Material and Methods

The experiment was carried out on 5 apparently healthy persons (mean age 33 years) and on 10 subjects (mean age 62 years) presumed to be atherosclerotic because of a history of myocardial infarction or of definite anginal symptoms with clear-cut electrocardiographic changes.

Blood specimens were obtained at hourly intervals during a period of 4 hours from the patients who had been fasting for at least 12 hours. Each specimen of blood was mixed with sodium oxalate and centrifuged for 15 minutes at 3,000 r.p.m. The optical density of the plasma thus separated was determined photometrically with a 640 mμ. filter; the determinations were made immediately and again after 20 hours at room temperature. The same procedure was repeated a few days later on the same subjects, who this time were given 250 mg. of gastric mucin prior to the experiment. The mean photometric readings for every hour in each group with and without gastric mucin are shown in figure 1.

Results

The optical density of fasting subjects, although it varied in the different individuals and at different times, remained unchanged throughout the period of observation. The densitometric curve was higher among the atherosclerotic than among the healthy subjects. Administration of gastric mucin was always followed by a reduction in plasma optical density. In both groups the maximal

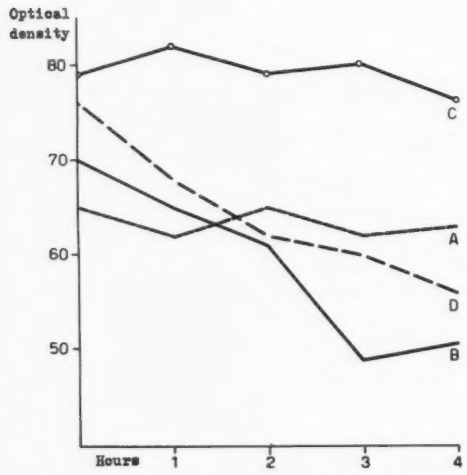

FIG. 1. Plasma optical density (mean values) in healthy subjects (*A* and *B*) and in atherosclerotic patients (*C* and *D*), without (*A* and *C*) and with (*B* and *D*) gastric mucin administration.

reduction occurred at the end of the third hour. The clearing effect was similar to that of heparin. Its magnitude at the end of the experiment, expressed in per cent of the optical density diminution, was 30 per cent for the healthy subjects and 26 per cent for the atherosclerotic patients.

The specimens kept at room temperature for 20 hours showed no significant changes in optical density in either group, whether or not the patient had received gastric mucin.

DISCUSSION

In accord with previous investigations,[2-4] gastric mucin showed in our experiment a constant and unequivocal effect on the plasma optical density, both in the healthy and the atherosclerotic groups, under basal conditions. The difference between the values (expressed in per cent of the optical density reduction) obtained in the 2 groups was not statistically significant. The clearing effect was similar to that of heparin in regard to constancy and degree, but differed insofar as it lasted longer and did not increase with the passage of time in vitro at room temperature.

The resemblance in the clearing activity of gastric mucin and of heparin is probably based on similarities in chemical constitution between the 2 compounds, such as a high hexuronic acid and glucosamine content.

We do not understand as yet the mechanism underlying the clearing effect of gastric mucin, nor do we know whether it is related to plasma and tissue factors as is, according to Anfinsen,[5] the heparin clearing factor. It seems likely, however, that the clearing power is not due to an enzymatic effect of the lipoprotein lipase type such as the one that is apparently responsible for the heparin clearing effect. Capraro and Cantone[6] suggest that the finding may be accounted for by an increase in the plasma lipodispersing activity that is enhanced by gastric mucin.

SUMMARY

A plasma-clearing effect was obtained by the oral administration of gastric mucin in a group of healthy subjects and another group of atherosclerotic patients under basal conditions. The magnitude of the clearing effect at the end of 3 hours was 30 per cent for the healthy subjects and 26 per cent for the atherosclerotic patients.

The similarities and differences between the heparin clearing effect and that of gastric mucin are discussed.

SUMMARIO IN INTERLINGUA

Un effecto clarificatori in le plasma esseva producite per le administration de mucina gastric in un gruppo de subjectos normal e in un secunde gruppo de subjectos atherosclerotic sub conditiones basal. Le magnitude del effecto clarificatori al fin de 3 horas esseva 30 pro cento in le caso del subjectos normal e 26 pro cento in le caso del subjectos atherosclerotic.

Es discutite le similaritates e le differentias inter le effecto clarificatori de heparina e illo de mucina gastric.

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An occasional observation of improvement of psoriasis in a patient being treated with Tromexan because of myocardial infarction is reported. In order to learn whether the improvement was coincidental or had other meaning, 17 patients with psoriasis have been treated with Tromexan or with Sintrom or Dicumarol; 3 of these did not respond to treatment, 8 showed regression, 6 became free of lesions. It was noted that the anterior surfaces cleared more rapidly than the posterior, and that the scalp cleared first while the legs were last. The time required for complete regression varied between 2 and 6 months. It was found that the therapeutic effect was obtained when a "threshold" dose was given; lower doses were ineffective, while larger single doses did not produce better results; repeated "threshold" doses (limited in number only by their anticoagulant effect) were more effective. Tromexan was commonly effective in single doses of 300 mg. and was better suitable for this purpose than comparably effective doses of Sintrom or of Dicumarol, because of its lower anticoagulant effect. There was no relation between the prothrombin level and the therapeutic result obtained. However, the use of antagonists to the anticoagulant (menaphthone), together with the drug, inhibited its beneficial effect.

Calabresi

Plasma Turbidity Changes and Electrocardiographic Alterations Induced by Alimentary Hyperlipemia in Anginal Patients before and after the Administration of Gastric Mucin

By VINCENZO RULLI, M.D., AND BALDO ROSSI, M.D.

The hyperlipemia induced by a fat meal in anginal patients is frequently associated with clinical and electrocardiographic changes suggesting transient coronary insufficiency. Gastric mucin administered to 10 anginal patients at the same time as a fat meal invariably prevented the hyperlipemia, evaluated as increase of plasma optical density, and in one half of the cases it reduced the magnitude of the electrocardiographic changes as compared with the changes found in control experiments. Gastric mucin therefore exerts a powerful antilipemic and clearing action. Its inhibitory effect on the electrocardiographic changes associated with alimentary hyperlipemia is less evident than that of heparin.

IN A previous paper[1] on plasma turbidity and electrocardiographic changes associated with alimentary hyperlipemia, we demonstrated that both the foregoing changes were inhibited when heparin was administered intravenously at the same time as the fat meal. We discussed in that paper the interpretation of this phenomenon and its possible relationship with the pathogenesis of postprandial angina and arterial atheroma.

Capraro and his associates,[5] Cresseri,[2–4] and Cantone,[7–9] as a result of their researches on the biologic properties of hog gastric mucin extracts, recently clarified some points of considerable interest concerning the effect of such extracts on certain plasma conditions that many investigators believe to be related with atherogenesis or with frank atheromatous conditions.

A variety of biologic properties has been ascribed to the mucin compound prepared from hog gastric mucosa. Among such properties are the capacity to bind vitamin B_{12} and thus render it undialyzable,[2–4] and to act as growth factor for *Lactobacillus bifidus*, var. Penn, an antianemic action in mice, rats,[5] and in human pernicious anemia,[6] a protective effect (even when given by mouth) against alimentary and toxic liver steatosis in guinea pigs and rats,[7] the capacity to enhance the plasma clearing power in the rabbit, and an antilipemic effect in rabbits[8] and men.[9] The 2 last-mentioned properties are of special interest and appear worthy of further investigation.

Because of the finding that in men and rabbits, gastric mucin administered by mouth increases the plasma clearing action on lipid substrates (emulsion of homogenized milk), the foregoing authors suspected that an acid

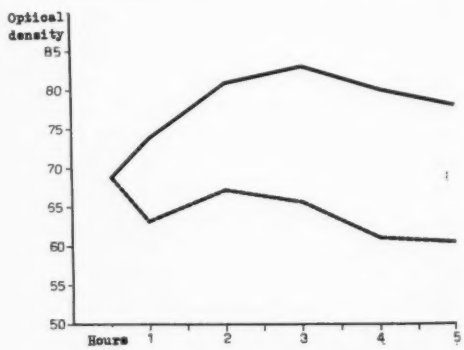

FIG. 1. Mean plasma turbidimetric curves after a fat meal consisting of 200 Gm. of milk cream (*solid line*) and after the same fat meal with the addition of 250 mg. of gastric mucin (*broken line*).

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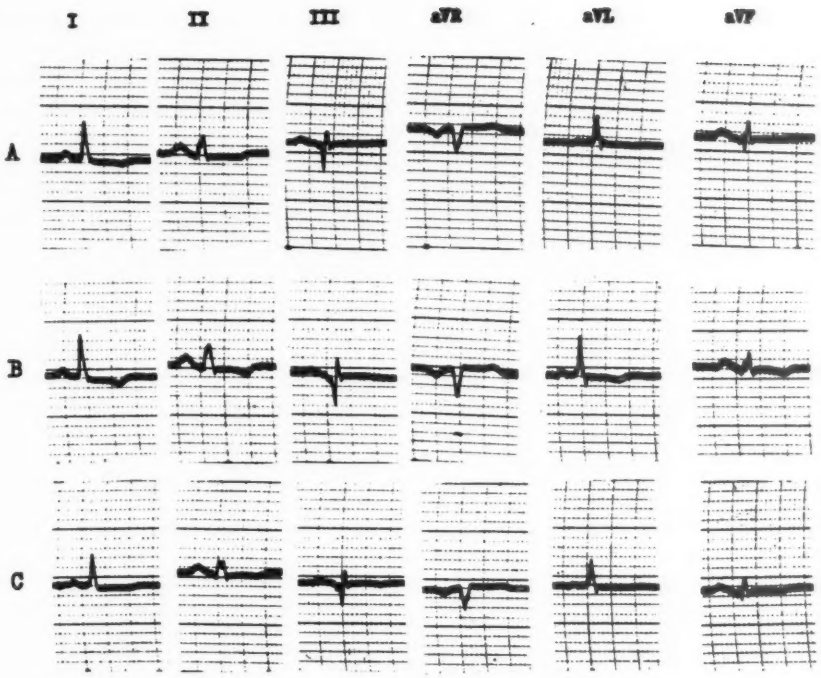

FIG. 2. Reduction by effect of gastric mucin of the electrocardiographic changes associated with a fat meal. *A*. Electrocardiogram recorded before the test: optical density 65. *B*. electrocardiogram recorded 3 hours after the fat meal without gastric mucin: optical density 75. *C*. Electrocardiogram recorded 3 hours after the fat meal with the addition of gastric mucin: optical density 60.

aminopolysaccharide, present in the gastric mucin preparation under study, might be responsible for this phenomenon, since it is known that an increase in the plasma clearing power may be obtained by the parenteral administration of sulfurated acid aminopolysaccharides (for example, heparin). They succeeded in isolating an acid aminopolysaccharide, composed essentially of d-glucuronic acid and d-glucosamine. Because of its physical and chemical properties, there is reason to believe that this substance is an acid aminopolysaccharide of the hyaluronic acid type, devoid of any appreciable anticoagulant effect, and active by mouth.

Cantone[8] made a comparative study of the clearing effect of heparin and of that of the acid aminopolysaccharides contained in hog gastric mucosa, and concluded that the mechanism of the clearing effect exerted by the plasma of animals treated with gastric mucin is different from the mechanism underlying the clearing effect of heparinized plasma. Cantone concluded that the clearing factor acting in the rabbit after the administration of gastric mucin does not belong to the same enzymatic type as heparin. On the other hand, just as the heparin clearing effect is inhibited by protamine sulfate, also the gastric mucin clearing effect is inhibited in vivo by the administration of protamine sulfate.[9]

In view of the interest aroused by heparin as a regulator of the chemicophysical state of plasma lipids, which many authors believe to be related to the problem of atherogenesis, we deemed it worthwhile to study the clearing effect of gastric mucin in human alimentary hyperlipemia, and to investigate whether

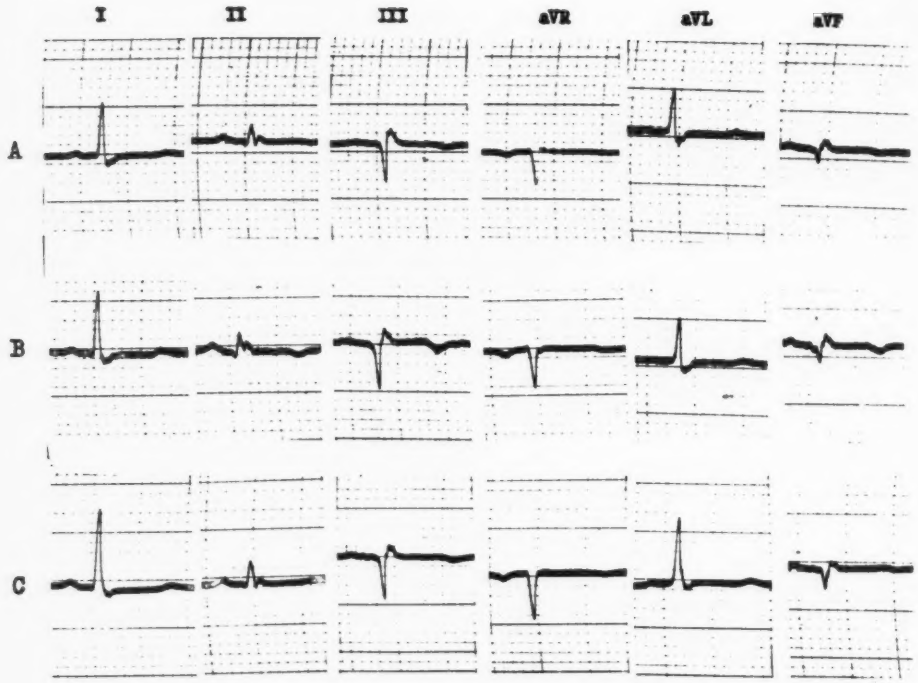

FIG. 3. Reduction by effect of gastric mucin of the electrocardiographic changes associated with a fat meal. *A*. Electrocardiogram recorded before the test: optical density 62. *B*. Electrocardiogram recorded 3 hours after the fat meal without gastric mucin: optical density 85. *C*. Electrocardiogram recorded 3 hours after the fat meal with the addition of gastric mucin: optical density 69.

this substance was capable to prevent the electrocardiographic changes noted in certain anginal patients after a fat meal.

MATERIAL AND METHODS

A total of 10 patients was selected on the basis of the following criteria: long-standing and typical manifestations of effort angina; electrocardiographic signs of coronary artery insufficiency at rest; absence of any digestive complaint; development of electrocardiographic alterations after a fat meal.

The plasma lipemia was evaluated as plasma optical density, determined photometrically in the fasting state and at hourly intervals for 5 hours after a fat meal. The fat meal consisted of 200 Gm. of homogenized milk cream containing 40 per cent of fat.

The electrocardiogram was recorded at basal rest in the fasting patient and every hour for 5 hours after the fat meal.

The same procedure was adopted for another experiment, carried out on the same patients, who this time received 250 mg. of gastric mucin by mouth at the same time as the fat meal. Every precaution was taken to ensure that the exploring electrode was always placed exactly on the same points over the precordial region.

RESULTS

Alimentary Hyperlipemia with and without Gastric Mucin Administration (Fig. 1). The turbidimetric curve expressing the plasma hyperlipemia induced in 10 patients by a fat meal began to rise 1 hour after the meal, attained its peak during the third hour, and subsequently descended.

When 250 mg. of gastric mucin were given together with the fat meal, the contour of the turbidimetric curve was completely different. The optical density did not increase but instead decreased gradually; toward the end

f the second hour there was a mild elevation, hich, however, never attained the pretest vel.

At the end of the experiment (5 hours after e fat meal), the optical density of the un- eated group was considerably higher than e initial value. In the treated patients, the asma was much clearer than before the test. he administration of gastric mucin, there- re, not only inhibited the hyperlipemia as- iated with a fat meal, but in addition even luced the plasma optical density existing fore the experiment.

Electrocardiographic Changes with and without Gastric Mucin Administration. The electrocardiographic changes associated with the fat meal were as a rule of minor degree. They consisted of reduced amplitude, diphasism (+ − or − +), T-wave inversion of bifidity in one or more left precordial leads, and correspondingly in leads I and/or II and aV_L or in leads III and/or II and aV_F, depending on the electrical position; the T-wave changes were often associated with slight S-T abnormalities. The electrocardiographic alterations usually appeared 1½ hour after the fat meal; their incidence was highest during the third hour; in a few instances only they had cleared up completely by the end of the experiment (fifth hour). The findings are in perfect agreement with our previous results.[1]

When gastric mucin was given simultaneously with the fat meal, 5 of the 10 patients showed electrocardiographic changes of the same type and degree as the untreated patients. In the 5 remaining patients the changes either did not appear or were negligible. The results are shown in figures 2 and 3.*

Discussion

Our findings agree with the observations reported by Capraro and associates and by Crosseri concerning the antilipemic effect of gastric mucin in the rabbit and its clearing effect on homogenized lipid substrates.

In every one of our patients the plasma optical density not only failed to increase after the fat meal, but actually diminished steadily under the influence of gastric mucin. The clearing effect is similar to that of heparin: because of this similarity and of certain chemical affinities, it is likely that the antilipemic effect is due to the action of the hexuronic groups present in both heparin and gastric mucin. The latter, however, has the practical advantage of being active even by mouth.

With regard to the electrocardiographic changes induced by alimentary hyperlipemia in anginal patients, we were unable to demonstrate that gastric mucin invariably inhibits such changes. Actually, only 5 of the 10 patients showed an appreciable reduction in the severity and duration of the changes as compared with the group not receiving gastric mucin. It seems, therefore, that the inhibitory effect of gastric mucin on the electrocardiographic alterations associated with a fat meal is less evident than that of heparin.[1, 10] This may support the hypothesis that the action of heparin is not confined to its antilipemic and clearing effects, but may include other more complex actions, as several authors have suggested.

Summary

Hyperlipemia was induced in 10 anginal patients by a fat meal consisting of 200 Gm. of milk cream with a 40 per cent fat content. The plasma lipemia, determined photometrically as plasma optical density, was measured at hourly intervals. Electrocardiograms were recorded in the fasting state and at hourly intervals after the fat meal. The patients who showed electrocardiographic changes after the fat meal were again submitted to the same test but in addition received 250 mg. of gastric mucin at the same time as the fat meal. Gastric mucin invariably inhibited the alimentary hyperlipemia and in one half of the cases reduced the electrocardiographic changes associated with hyperlipemia.

Summario in Interlingua

Hyperlipemia esseva inducite in 10 patientes anginal per medio de un repasto grasse

*Only the peripheral leads are shown because the chest leads are not more informative.

consistente de 200 g de crema de lacte con un contento de 40 pro cento de grassia. Le lipemia del plasma esseva mesurate a intervallos de un hora per determinar photometricamente le densitate optic del plasma. Electrocardiogrammas esseva obtenite in stato jejun e a intervallos de un hora post le ingestion del repasto grasse. Le patientes qui exhibiva alterationes electrocardiographic post le repasto grasse esseva resubmittite al mesme test, sed nunc illes recipeva additionalmente 250 mg de mucina gastric, administrate simultaneemente con le repasto de grassia. Mucina gastric inhibiva invariabilemente le hyperlipemia alimentari, e in un medietate del casos illo reduceva le alterationes electrocardiographic associate con le hyperlipemia.

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Burch, G. E., and Hyman, A.: Influence of a Hot and Humid Environment upon Cardiac Output and Work in Normal Man and in Patients with Chronic Congestive Heart Failure at Rest. Am. Heart J. **53**: 665 (May), 1957.

Measurements of the cardiac output by the direct Fick principle utilizing cardiac catheterization in control subjects and patients with chronic congestive heart failure showed that exposure to a hot and humid environment increased the cardiac output, stroke volume of the ventricle, mechanical, and physiologic cardiac work, and tension upon the walls of the ventricles in both groups. There was less of an increase in the patients with congestive heart failure than in the control subjects. The increase in cardiac work and output was found to occur more as a result of a larger stroke volume than greater cardiac rate. The therapeutic implications of the observed stressful cardiac responses to a hot and humid environment are discussed.

Sagall

Persistent Right Jugular Lymph Sac Simulating Cervical Tumor

By Israel S. Steinberg, M.D.

A patient who had had trauma to the right shoulder and upper chest complained of a right supraclavicular mass. Examination revealed a cystic tumor made larger by performance of the Valsalva maneuver. Angiocardiography demonstrated that there was partial stenosis of the terminal end of the right innominate vein. This and the Valsalva maneuver were responsible for the filling of a right persistent jugular lymph sac that simulated a cervical tumor.

COMMUNICATION of the subclavian vein with a persistent jugular lymph sac is very rare. Indeed, only one other case recently reported by Deaton[1] is recorded in the literature. Deaton's patient, a 5-year-old girl, had had a right supraclavicular cystic mass upon performance of the Valsalva maneuver. At operation an abnormal vascular channel was found and excised. Histologic study suggested that it was either a vein or mixed venous and lymph channel.

In the case herein reported, trauma to the right side of the neck and upper chest was followed by the development of a large right supraclavicular mass. Angiocardiographic studies demonstrated that the right jugular veins were opacified and a large venous channel became markedly distended during the Valsalva maneuver due probably to partial thrombosis of the distal portion of the right innominate vein. The supraclavicular mass was caused by the abnormally dilated venous channels.

Case Report

A 50-year-old electrician (N.Y.H. #731658) was admitted on February 16, 1956, with the chief complaint of a lump in the right side of the neck. The patient claimed that he was well until December 8, 1954, when on completion of the day's work, he grasped a block and tackle weighing 75 pounds and swung it on his right shoulder. Then, with a combination lifting and throwing motion, he transferred the apparatus from his shoulder to beneath a table. Suddenly he experienced pain in the right supraclavicular area and for about 25 minutes was unable to "straighten up." Subsequently, there was pain along the right parasternal area and when he looked into a mirror, he discovered for the first time that a "lump" had appeared in the right side of the neck. Since then, the patient has continued to have right supraclavicular and parasternal pain of a throbbing character in the right paratracheal and temporal regions. The bulge in the right neck persisted and was made larger by bending and straining movements. Dizziness, syncope, paresthesia, and anesthetic sensations were denied.

Fig. 1. Photograph of artist's drawing of a large right supraclavicular cystic mass during the Valsalva maneuver.

On examination, the patient was thick set, well developed and nourished, and in no discomfort. The only abnormal finding was a nontender, soft, cystic, nonrepitant, and nonpulsatile mass about 3 by 3 cm. in diameter located in the right supraclavicular area. It was observed that while demonstrating the mass the patient performed the Valsalva maneuver. Indeed, it reached its maximum size (about 5 by 5 cm.) (fig. 1) during this

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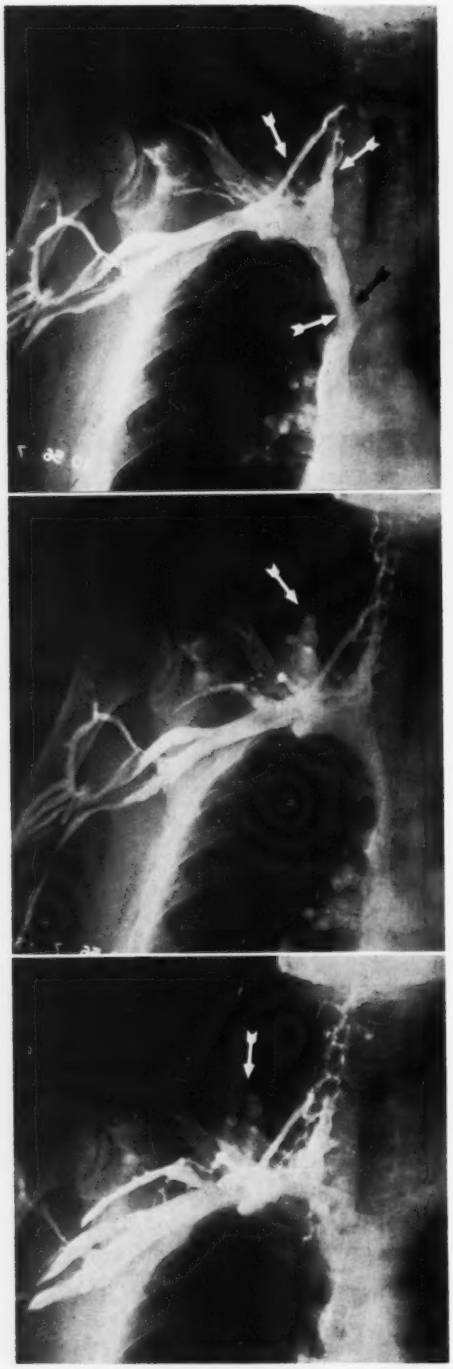

FIG. 2 *Top.* Angiocardiography 2 seconds after the beginning of injection and during mild inspiration reveals opacification of the right axillary, subclavian, innominate veins and the superior vena cava. Note narrowing of the right innominate vein, becoming abrupt at entrance into superior vena cava (*arrows*). Upper arrows point to the external and internal jugular veins. *Middle.* One second later, when patient has begun performing the Valsalva maneuver, the axillary and jugular veins are markedly distended. A large paired venous channel (*arrow*) arising from the right subclavian vein and lateral to the jugulars is evident. *Bottom.* At the height of the Valsalva maneuver, 6 seconds after beginning of injection, opacification of the persistent jugular lymph sac is still present (*arrow*); the axillary and subclavian veins are dilated.

FIG. 3. Lateral angiocardiogram reveals pronounced narrowing of the right innominate vein as it enters the superior vena cava (*arrows*).

time. No bruits were heard over the mass or neck. The cardiovascular system was otherwise normal. Venous distention of the thorax was not found. Blood pressure readings were 132/92 in the right arm and in the left, 130/90 mm. Hg. The pulses were equal and unaltered by movements of abduction or hyperabduction. Laboratory examinations including electrocardiographic studies were normal. Conventional and laminographic x-ray examinations of the chest and neck did not reveal cervical, mediastinal, or pulmonary masses other than the supraclavicular lesion.

Angiocardiographic studies were made on February 20 and 23, 1956. Serial frontal films at 1-

seconds intervals were taken with the patient supine on a roll-film magazine. At first, with gentle inspiration, the veins of the right side of the neck were seen to fill from the right subclavian vein (fig. 2*A*). Later, at about 3 seconds after the beginning of injection, the patient was observed to be performing the Valsalva maneuver; at this time, large abnormal veins in the right subclavian area became evident (fig. 2 *B*). The right innominate vein was slightly diminished in caliber but at its terminal end it appeared narrowed, rigid, and poorly opacified (fig. 2*A* and *B*). In the lateral, erect view (fig. 3) the narrowing and rigidity of the terminal end of the right innominate vein was even more striking. Angiocardiography via the opposite arm in the supine position disclosed a normal left innominate vein (fig. 4).

After discharge, attempts to have the patient return for further observation and treatment were unsuccessful. Recent communication with the patient revealed that although the cervical swelling and symptoms persisted, he had not lost time from work. Indeed, he stated that he felt so well that he was reluctant to take time off from work for re-examination.

Discussion

The development of the lymphatic system is a fascinating study. Up to the beginning of the twentieth century, the lymphatics were believed to be of mesenchymal origin (tissue spaces and serous cavities). Largely due to the American anatomists, Sabin[2-4] and Lewis,[5, 6] it became established that the lymphatics were derived from veins. In animals the lymphatic system begins as a series of 8 sacs. Three are paired, the jugular, subclavian and posterior lymph sacs, while 2 are unpaired, the retroperitoneal and cisterna chyli.[2-7] In the human embryo, there are only 6 lymphatic sacs, the subclavian being extensions of the jugular. Only the jugular sacs retain connections with their parent veins; the others forming in regions where there is great shifting of veins do not have secondary communications with their own veins but join with the other lymph sacs to establish an independent system.[4, 6]

Thus, by the end of the ninth week, the adult pattern of the lymphatic system can be recognized. The thoracic duct is a long continuous channel which at its cephalic end communicates freely with the jugular lymph sac in the left side of the body and enters the left innominate vein at the junction of the jugular and subclavian veins (the venous angle). Similarly, the right jugular lymphatic trunk opens into the right innominate vein at the junction of the right subclavian and jugular veins. Well formed valves at the site of entrance of the lymphatic channels into the veins ordinarily prevent reflux of blood into the lymphatic system.[8]

Fig. 4. Angiocardiogram, ½ second after injection via the left arm, shows the left subclavian and innominate veins to be of normal caliber and there is no reflux filling of collateral veins. Later films showed blood flow into the superior vena cava to be normal.

Apparently, in the patient described above, as well as in Deaton's case,[1] persistence of the right jugular lymph sac and damage or absence of the valve at the site of junction with the veins resulted in the appearance of the supraclavicular mass. Retrograde filling of the jugular sac was also aided by partial stenosis of the terminal end of the right innominate vein and the Valsalva maneuver.

Alteration of blood flow into the heart during the Valsalva maneuver has been admirably demonstrated by venography by Candel and Ehrlich.[9] Similarly, during inspiration for the method of angiocardiography, if the Valsalva maneuver is performed, (and often it is done unknowingly by the patient) blood flow into the heart via the great veins of the neck and arms may be almost completely shut off. As a result marked dilatation of the subclavian and cephalic veins with reflux into the shoulder and jugular veins may be demonstrated. Indeed, performance of the Val-

salva maneuver may interfere with the successful performance of intravenous angiocardiography because the delay in passage of contrast material into the cardiac chambers and great vessels results in faulty timing and poor opacification of the cardiovascular structures.[10]

Apparently, in the case reported above, trauma to the right side of the neck and upper chest was followed by the appearance of a mass in the right supraclavicular area. Whether it existed before the injury could not be determined. In any event, it was at that time that the patient discovered the mass and that it became larger on straining. Consequently, in order to observe it, he habitually performed the Valsalva maneuver and was rewarded by the appearance of the mass. It appears, however, that the marked dilatation of the right jugular sac was not due to the Valsalva maneuver alone; the partially thrombosed distal end of the right innominate vein by impeding blood flow into the heart apparently also played a significant role. In this case, angiocardiography established the vascular nature of the cervical tumor and excluded other causes of cervical masses such as enlarged lymph nodes, neoplasms, and cervical cysts (thyroglossal, branchial, hygromatic, and bronchogenic).[11-13] Angiocardiography also differentiated the mass from brachiocephalic arterial abnormalities such as aneurysms and buckling.[10, 14, 15]

Excision of a persistent jugular lymph cyst, principally for cosmetic purposes, seems warranted. In Deaton's case such treatment was curative.[1] In the case herein described, surgery would also have permitted inspection and palpation of the great veins and established with certainty whether or not the apparent stenosis of the terminal end of the right innominate vein really existed or was associated with the physiologic changes produced by the Valsalva maneuver.

Summary and Conclusions

Angiocardiography established that a large right supraclavicular cystic mass appearing during the Valsalva maneuver in a patient who had had trauma of the right shoulder and upper thorax was due to a dilated persistent jugular lymph sac. Partial thrombosis of the terminal end of the right innominate vein was also demonstrated and may have been a factor in causing reflux filling of the sac with blood. Thus, a rare and unique cause of a vascular cervical mass was established.

Acknowledgment

Thanks are due to Dr. Irving S. Wright for referring and giving permission to report this case.

Summario in Interlingua

Esseva establite per medio de angiocardiographia que un grande massa cystic dextro-supraclavicular, manifeste in le manovra de Valsalva in un patiente qui habeva habite trauma del spatula dextere e del thorace superior, indicava le presentia de un persistente dilatation de un sacco lymphatic jugular. Thrombose partial del extremitate terminal del vena innominate dextere esseva etiam demonstrate e representava possibilemente un factor in causar le plenation del sacco per un refluxo de sanguine. Assi un rar o unic causa de un massa vasculo-cervical esseva establite.

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Abrams, H. L.: Radiologic Aspects of Operable Heart Disease. III. The Hazards of Retrograde Aortography: A Survey. Radiology **68**: 812 (June), 1957.

Twenty-nine deaths were recorded in a series of 1,706 thoracic aortographic examinations. Use of a 70 per cent concentration was fatal 8 times more frequently than when a 30 or 35 per cent concentration was employed. Retrograde carotid injection was attended by a higher mortality than brachial or catheter injection. No deaths followed the use of retrograde brachial aortography with 30 to 35 per cent media. Most of the deaths and severe reactions appeared to be associated with cerebral damage. Less frequent were renal, cardiac, and respiratory complications. The author recommends that in children under the age of 4 lesser concentrations be employed; in adults 20 to 30 ml. of a 70 per cent agent is relatively safe. The use of a general anesthetic increases the hazards. The roles played by catheter positioning, patient's state of hydration, electrocardiographic monitoring and sensitivity testing are discussed.

SCHWEDEL

The Deep S Wave in Leads V_1, V_2, and V_3 in Right Ventricular Hypertrophy

By HERBERT SHUBIN, M.D., AND DAVID C. LEVINSON, M.D.

Six patients with mitral stenosis, 3 with pulmonic stenosis, and 1 with pulmonary hypertension are presented. All had isolated right ventricular hypertrophy and all had deep S waves in V_1, V_2, or V_3. In 3 cases the voltage of R in V_1 was less than 0.5 millivolt. In 3 cases R/S ratios in V_1 of less than 1.0 were present. Vectorcardiograms showed characteristic features and illustrated the reasons for the electrocardiographic findings.

THE presence of a deep S wave in leads V_1 or V_2 is often interpreted as evidence suggesting left ventricular hypertrophy. Since the maximal electric force in left ventricular hypertrophy usually moves to the left and posteriorly, the presence of a deep S wave in leads V_1 or V_2 often correlates well with this condition.

In the interpretation of hypertrophies of congenital or acquired heart disease, the presence of a deep S wave in V_1 or V_2 may, however, not be due to left ventricular hypertrophy, either isolated, or in combination with right ventricular hypertrophy.

Ten cases of isolated right ventricular hypertrophy in which deep S waves were present in either V_1, V_2, or V_3 have been reviewed. There were 6 patients with pure mitral stenosis, 3 with isolated pulmonic stenosis, and 1 with "primary" pulmonary hypertension. The mitral stenosis cases were diagnosed by cardiac catheterization (table 1), and were confirmed at surgery in 4 instances. Subsequently one of these was also confirmed at autopsy and had right ventricular hypertrophy, but no left ventricular hypertrophy. Of the 3 cases with isolated pulmonic stenosis 2 were diagnosed at cardiac catheterization (table 1), and confirmed later at surgery. The third case of pulmonic stenosis was a relatively mild one and was diagnosed by cardiac catheterization alone (table 1). The single case of "primary" pulmonary hypertension was diagnosed at cardiac catheterization.

TABLE 1.—*Hemodynamic Findings at Cardiac Catheterization*

Case	Age	Diagnosis	Pressures (mm. Hg)			Cardiac index
			Right ventricle	Main pulmonary artery	Peripheral pulmonary artery	
1	33	Mitral stenosis	115/10	115/55	—	1.5
2	52	Mitral stenosis	110/10	110/50	—	1.7
3	44	Mitral stenosis	104/16	104/52	25/22	1.5
4	36	Mitral stenosis	84/10	80/44	25/20	1.9
5	54	Mitral stenosis	60/6	60/25	25/18	1.9
6	49	Mitral stenosis	47/2	47/32	26/23	2.2
7	45	"Primary" pulmonary hypertension	125/10	130/50	11/7	2.9
8	11	Pulmonic stenosis-infundibular	120/6	22/17	—	3.3
9	8	Pulmonic stenosis-valvular	78/12	17/10	—	3.7
10	10	Pulmonic stenosis-valvular	40/4	15/5	—	3.1

Electrocardiograms

The electrocardiograms on these patients are shown in figure 1. Noteworthy here are the deep S waves in V_1, V_2, or V_3. Of the 6 cases with mitral stenosis the R/S ratio in V_1, V_{3R}, and V_{4R} was greater than 1.0 in all instances. Of the 3 cases with pulmonic stenosis the R/S ratio in V_1 was less than 1.0 in 2 instances, but reached 1.0 in either V_{3R} or V_{4R}. Similarly in the case with "primary" pulmonary hypertension the R/S ratio, although less than 1.0 in V_1, was 1.0 in V_{4R}.

In 7 of the 10 cases the R wave in V_1 was

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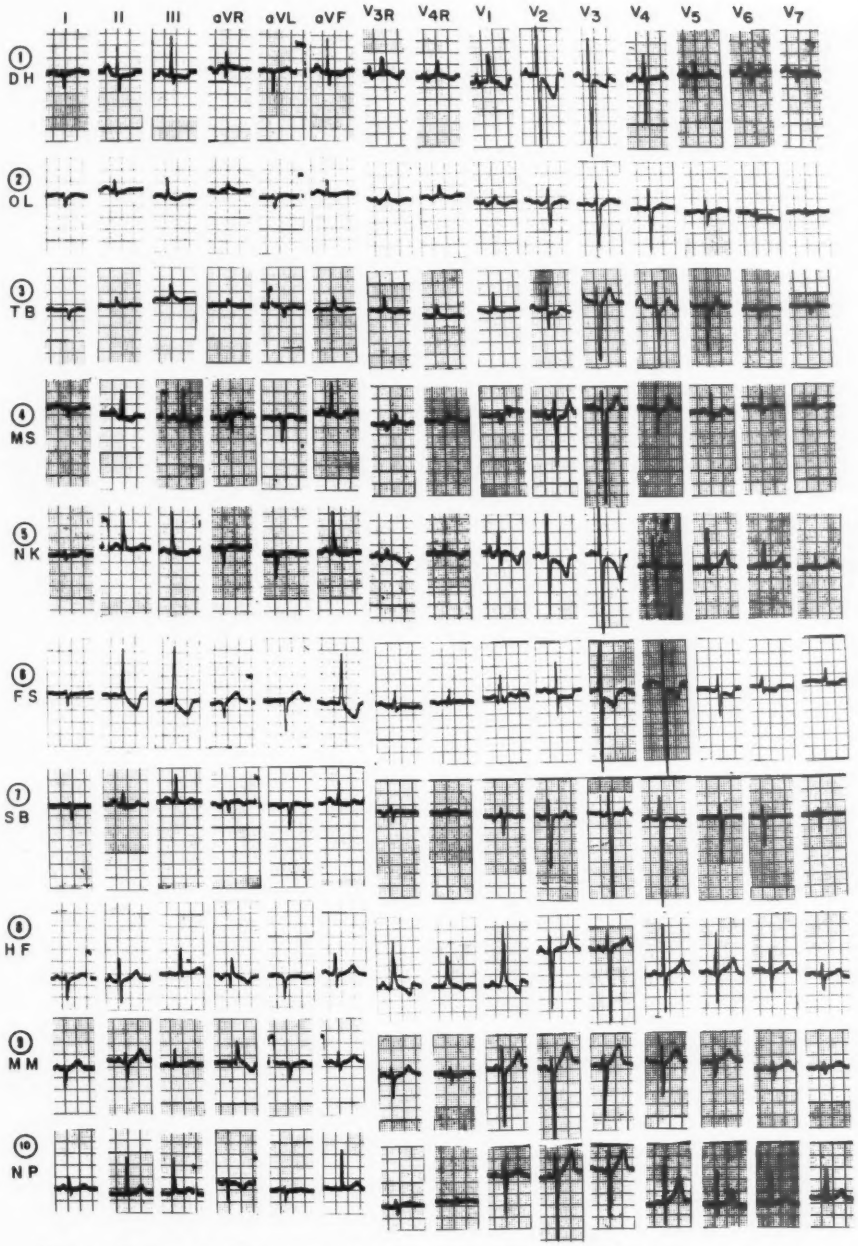

FIG. 1. Electrocardiograms on cases 1-6 are on patients with mitral stenosis, case 7 is on a patient with pulmonary hypertension, and cases 8-10 are on patients with pulmonic stenosis.

eater than 0.5 millivolt. In 2 patients the in V_1 was 0.25 millivolt and in another 30 millivolt.

R waves in aV_R of more than 1 millivolt were present in only 5 of the 10 cases. In 3 cases there were no R waves in aV_R.

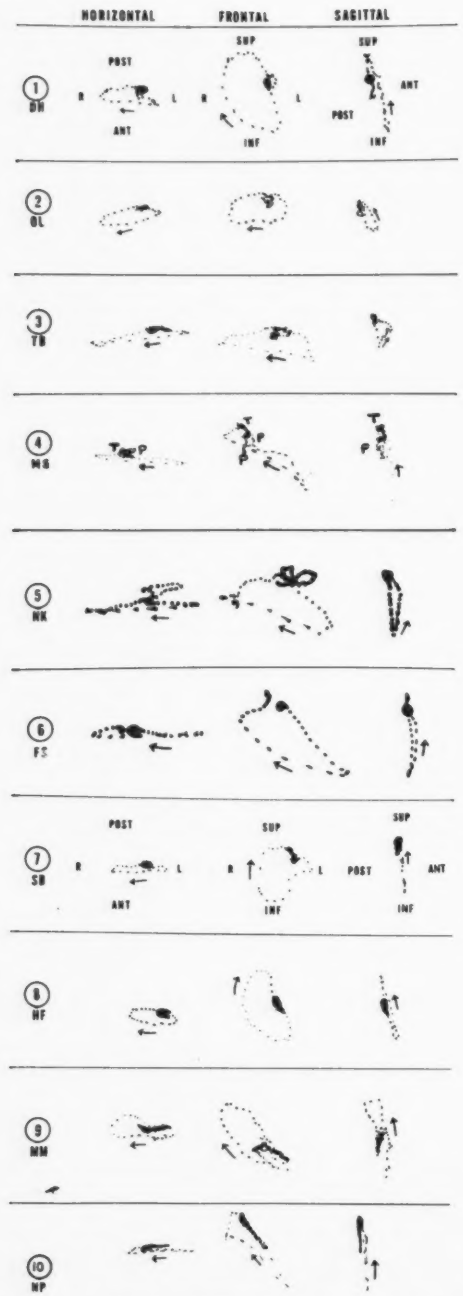

FIG. 2. Vectorcardiograms on cases 1-6 are on patients with mitral stenosis, case 7 is on a patient with pulmonary hypertension, and cases 8-10 are on patients with pulmonic stenosis. *Arrow*, direction of inscription of vectorcardiographic loops.

In all 4 of the cases with mitral stenosis in whom a sinus rhythm was present, the P waves in V_1, V_{3R}, and V_{4R} were diphasic, with a plus minus configuration. In 1 instance (case 4), the amplitude of the P waves in V was greater than the RS. In the 3 cases of pulmonic stenosis, by contrast, only upright P waves were recorded in these leads. In the case with pulmonary hypertension only a negative P wave was recorded in V_1, V_{3R}, or V_{4R}.

In all but 2 instances the T waves in V_1 were negative. Those with positive T in V_1 were both in patients with pulmonic stenosis in whom the systolic pressure was less than 80 mm. Hg. Also noteworthy in these 2 cases was the age of the patients, one 10 years and the other 8 years, the youngest in the group. The 6 patients with mitral stenosis all had negative T waves in V_1, but all were receiving digitalis.

The T waves in V_6 were upright in 7 of the 10 cases. In the 2 cases where T in V_6 was flattened or diphasic, both patients were receiving digitalis.

The electrocardiographic axis was +90° or greater in 9 of the 10 cases. In the 1 instance in which the electrocardiographic axis was normal, the right ventricular pressure was 40/4 mm. Hg.

Vectorcardiograms

The vectorcardiograms on these patients are shown in figure 2. These were recorded by the cube system.

In the horizontal plane clockwise rotation of the loop was present in all cases. In 2 cases there were figure-eight loops; however the inscription was predominantly in a clockwise direction. The loops were deviated anteriorly and to the right in all cases except 1 (case 9) in which both anterior and posterior deviation was present.

In the frontal plane there was clockwise rotation of the loop in all instances. In the 6 cases of mitral stenosis the mean frontal axis was greater than +110° in 3 cases. In the 3 cases of pulmonic stenosis the mean frontal axis was greater than +110° in 2. In the single case with primary pulmonary hy

pulmonary hypertension the mean frontal axis was greater than +110°.

In the sagittal plane there was counterclockwise rotation in 6 cases and figure-eight loops in 4. Three of the mitral cases showed counterclockwise rotation of the loop, while 3 showed a figure-eight loop. In the pulmonic stenosis cases the loop rotated counterclockwise in 2 instances, and had a figure-eight configuration in the other. In the case with primary pulmonary hypertension the rotation was counterclockwise. The loop was deviated anteriorly in all cases except 1 (case 9) in which both anterior and posterior deviation were present.

The P wave is best shown in case 4, where it has been labeled (fig. 2). Here the loop lies posterior, predominantly to the left and inferior to the E point.

Discussion

Electrocardiograms

The deep S wave in lead V_1 may be found in left ventricular hypertrophy, in transmural septal myocardial infarction, and in chronic cor pulmonale.

The presence of a deep S in V_1 is often found in left ventricular hypertrophy. To be diagnostic of left ventricular hypertrophy, however, the S in V_1 voltage plus the R in V_5 or V_6 voltage should exceed 35 mm.[1] In the present report a total combined voltage of this magnitude was not present in any of the cases.

Transmural septal myocardial infarction may also be associated with a small R wave in lead V_1 and deep S waves in V_{1-3}. The electrocardiogram here may closely resemble that of left ventricular hypertrophy.[2]

The presence of deep S waves in V_1 and across the left precordium in chronic cor pulmonale has been stressed by Sodi-Pallares[3] and Sokolow and Lyon.[4] They note that the R wave may be small in all the precordial leads or may be absent in the right precordial leads. Sodi-Pallares attributes these R- and S wave changes to the abnormal vertical and low position of the heart.

Aside from chronic cor pulmonale, the presence of a deep S wave in lead V_1 or V_2, usually is not associated with right ventricular hypertrophy although Lasser and co-workers[5] and Donoso and associates[6] noted its presence in the right ventricular hypertrophy of congenital heart disease. The criteria for right ventricular hypertrophy of a number of authors[4, 7, 8] include an R/S ratio in V_1 which is 1.0 or greater. By this criterion alone 30 per cent of the patients in this report would not have been diagnosed as having right ventricular hypertrophy. If an R/S ratio of 1.0 or greater in either V_1, V_{3R}, or V_{4R} were regarded as evidence for right ventricular hypertrophy, then all 10 cases would have been so diagnosed. However, for reasons that are more apparent by vectorcardiographic analysis, it is quite possible that the R/S ratio in these leads may be less than 1.0 and right ventricular hypertrophy may still be present.

Vectorcardiograms

The orientation and direction of inscription of the vectorcardiographic loops are of considerable assistance in determining the presence of hypertrophy, either right, left, or combined.

Horizontal Plane

Clockwise or figure-eight rotation of the horizontal loop usually indicates right ventricular hypertrophy provided the QRS duration is less than 0.12 second. Clockwise or figure-eight rotation may occur with myocardial infarction,[8] especially when the duration of the QRS is 0.12 second or more. In our series clockwise rotation of the horizontal loop was present in all but 2 cases, where there was a figure-eight configuration. In no instance did the duration of the QRS exceed 0.12 second.

The deep S waves in V_1, V_2, or V_3, which characterized this series, need not be present in all stages of right ventricular hypertrophy. Figure 3 shows the vector loops in varying degrees of right ventricular hypertrophy. The relationship of the V_1, V_2, or V_3 electrodes to the E point, illustrates why the depth of the S wave varies so considerably. V_1 and V_2 are essentially anterior to the usual

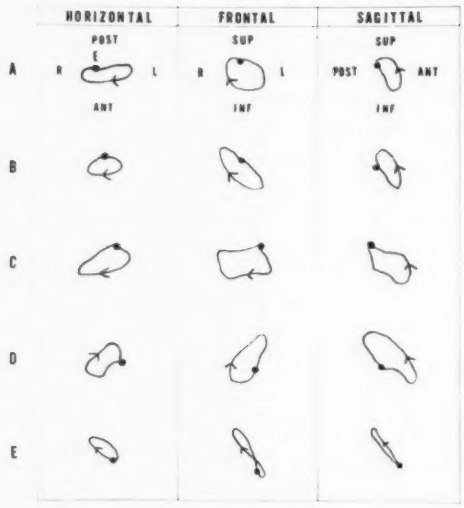

FIG. 3. The vectorcardiographic loops *A* through *E* are on cases with progressively more marked right ventricular hypertrophy. *Arrow*, direction of inscription of the vectorcardiographic loop.

location of the E point, but lie 10° to either side of the midline of the chest. Thus displacement of the vector loop anteriorly, as occurs in early right ventricular hypertrophy, will be associated with increased positive voltage in V_1 and V_2. S waves will occur if the vector loop moves posteriorly, as occurs in more advanced right ventricular hypertrophy.

The areas of positivity and negativity may be determined in the following manner (fig. 4): a line is drawn from the V_1 position through the E point (*X* line or axis of derivation). A second line (*Y* line) is drawn at a right angle to the *X* line, through the E point. Points that lie on the far side of this *Y* line are in the zone of negativity, and on the proximal side of the *Y* line in the zone of positivity. The solid vector loop in figure 4, which is taken from case 8, lies entirely on the positive side of the *Y* line, and thus only an R wave would be recorded in V_1. The dotted vector loop, which is taken from case 9, lies on both the positive and negative sides of the *Y* line and thus both R and S waves would be recorded in V_1 with this loop.

In all 6 mitral stenosis cases there is an abrupt increase in the size of the S wave between leads V_1 and V_2. From the V_2 position a much larger portion of the vector loop lies on the negative side of the *Y* line, than in V_1. The reason for this is illustrated in figure 5. Here the axis of derivation from the V_1 position is labeled *X* and the axis of derivation from the V_2 position *X'*. The corresponding *Y* and *Y'* lines are drawn at right angles to the *X* and *X'* lines, through the E point. The vector loop, which is taken from case 8, lies entirely on the positive side of the *Y* line, and thus only an R wave is recorded from the V_1 position. The same vector loop, however, lies on both the positive and negative sides of the *Y'* line, and thus both R and S waves are recorded from the V_2 position.

The depth of the S wave from the V_2 position thus depends on the amount of the vector loop that lies both to the right and posteriorly. If the vector loop is deviated markedly to the right and anteriorly, the S wave in V_2 may be very small, since only a small part of the vector loop would lie on the negative side of the *Y'* line.

Similarly, it is possible to have marked rightward deviation of the vector loop and a small R wave in V_{3R} or V_{4R}, provided the loop is inscribed significantly posteriorly. This is illustrated in case 9, where the posterior location of the loop largely cancels out the large positive wave that would be expected from its marked rightward location.

The presence, in 3 cases, of R (or R') in V_1 less than 0.5 millivolt in amplitude, is at variance with one of Milnor's[4] criteria for right ventricular hypertrophy. In case 7 the R wave in V_1 is 0.25 millivolt. The evidence for right ventricular hypertrophy in this case is (1) the presence of ventricular lift at the left sternal margin, (2) a pulmonary artery pressure of 130/50 mm. Hg, (3) a horizontal vector loop with clockwise inscription and with deviation to the right and anteriorly, (4) a frontal vector loop with clockwise inscription and a mean axis of +110°, (5) a sagittal vector loop with counterclockwise inscription and anterior deviation.

Inspection of the horizontal vector loop in

th case (case 7) shows the reason for the sm ll R wave in V_1. Although the loop is in ribed in a clockwise direction, and far to th right, it lies only slightly anterior to the E oint, hence the relatively small R in V_1. T placement of the electrodes in the various sy ems currently in use in vectorcardiograph does not represent an ideal method for th evaluation of the electric forces of the he rt. But even with such deficiencies as are pr sent with the various vectorcardiographic el ctrode-placement methods, the inscription and location of the loops help to clarify puzzling electrocardiographic variations.

Thus, even in the presence of large electric forces to the right, if these forces are sufficiently posterior, the R wave in V_1, V_{3R}, and V_{4R} may remain sufficiently small, or the S wave in these leads sufficiently large so that an R/S ratio of 1.0 or greater is never reached. From analysis of such vector loops, it is our opinion that an R/S ratio of 1.0 or greater in V_1, V_{3R}, or V_{4R} need not always be present for an electrocardiographic diagnosis of right ventricular hypertrophy.

Deep S waves in leads V_1 or V_2 may be produced by vectors oriented to the left, or to the left and posteriorly. Figure 6 illustrates the electrocardiogram and vectorcardiogram of a patient with isolated left ventricular hypertrophy due to a systemic hypertension. The deep S waves in V_1, V_2, or V_3, which are present here, may also be found in right ventricular hypertrophy. The tall R waves in V_5 and V_6 however are characteristic of left ventricular hypertrophy.

Diphasic P waves in leads V_1 or V_2 are found in certain cases of mitral stenosis (fig. 1, cases 1, 2, and 5). The diphasic P waves in these instances are due to hypertrophy of the left atrium, which causes the P vector loop to move posteriorly and to the left from its normal position.[9] This is illustrated in case 4 (fig. 2), where the P vector loop has been labeled.

Frontal Plane

In right ventricular hypertrophy the mean frontal plane axis may commonly be between

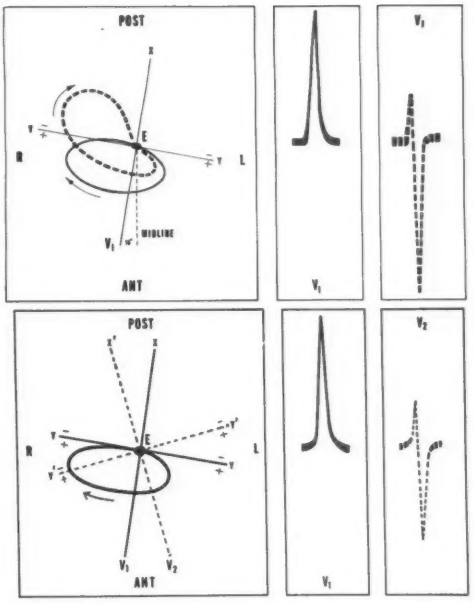

FIG. 4 *Top.* The method for derivation of the electrocardiogram from the horizontal vectorcardiographic loops is shown. The solid-line electrocardiogram is derived from the solid-line vectorcardiogram, and the dotted-line electrocardiogram from the dotted-line vectorcardiogram. Both these electrocardiograms are recorded from the V_1 position.

FIG. 5 *Bottom.* A single vectorcardiographic loop in the horizontal plane is shown. The solid electrocardiogram is derived from the V_1 position and the dotted-line electrocardiogram from the V_2 position. The *X* and *Y* reference lines relate to the V_1 position and the *X'* and *Y'* reference lines relate to the V_2 position.

+110° to ±180° or −91° to ±180°. A mean frontal plane axis of less than +110°, however, does occur in right ventricular hypertrophy,[8] and was present in 40 per cent of the patients in this report. Clockwise rotation of the frontal loop was present in all instances.

A tall R wave in lead aV_R is found when a significant part of the vector loop lies on the positive side of a line extending from +120° through the E point to −60°. Case 9 illustrates this point. The major part of the loop lies at about −150° (i.e. on the positive side of the *Y* line for lead aV_R) and the R wave in aV_R measures 8 mm.

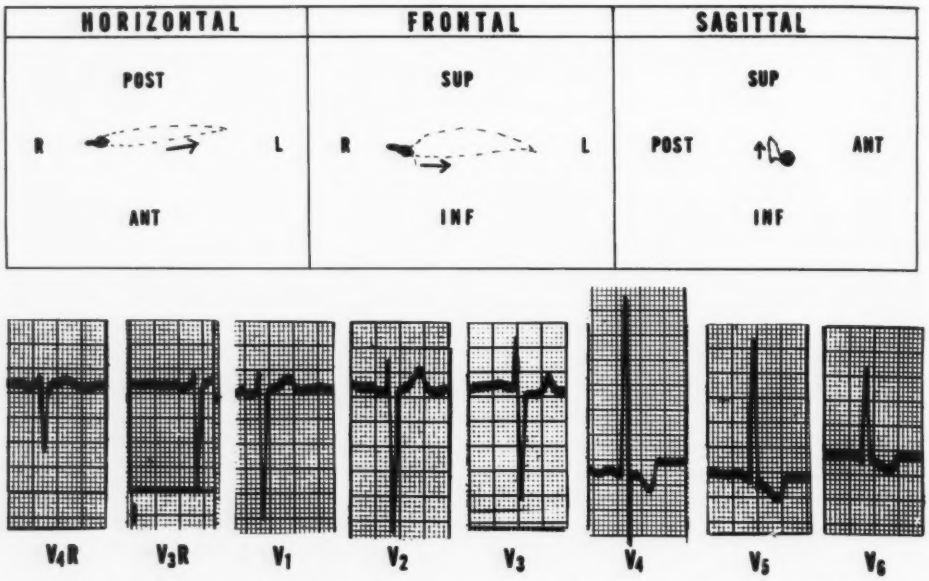

FIG. 6. The vectorcardiogram and electrocardiogram are shown in a case of left ventricular hypertrophy.

In 3 of the cases there is no R wave in aV_R. The evidence for isolated right ventricular hypertrophy in 2 of these, (case 5 and 6) is (1) the presence of the diastolic rumbling apical murmur of mitral stenosis and of a mitral opening snap, (2) the absence of the systolic murmur of mitral insufficiency, (3) an accentuated P_2, (4) an elevated wedged pulmonary artery pressure, (5) the absence of a regurgitant *V* wave in the wedged pulmonary artery pressure tracing, (6) the presence of moderate pulmonary hypertension, (7) left atrial and pulmonary artery enlargement by x-ray, (8) tall R waves in lead V_1 and with R/S ratios greater than 1.0, (9) horizontal vector loops with clockwise inscription and with deviation to the right and anteriorly, (10) sagittal vector loops with counterclockwise inscription and anterior deviation. The evidence for right ventricular hypertrophy in the third case (case 7, "primary" pulmonary hypertension) has been previously presented in detail.

The findings in these 2 cases of mitral stenosis and in the single case of "primary" pulmonary hypertension provide pertinent evidence for right ventricular hypertrophy, despite the absence of R waves in lead aV_R.

SUMMARY

Six cases with mitral stenosis, 3 with pulmonic stenosis, and 1 with pulmonary hypertension have been described. In all 10 cases there was isolated right ventricular hypertrophy, and in all of them deep S waves were present in V_1, V_2, or V_3.

R/S ratios of less than 1.0 in V_1 were present in 3 cases. The voltage of R in V_1 was less than 0.5 millivolt in 3 cases. R waves were absent in aV_R in 3 instances.

Vectorcardiograms on these patients showed right ventricular hypertrophy and illustrated the reasons for the electrocardiographic findings.

ACKNOWLEDGMENT

The authors gratefully acknowledge the assistance of Mrs. Rita Shulman, Mrs. Ella Washington, and Mr. Ernest Valenzuela.

SUMMARIO IN INTERLINGUA

Es describite 6 casos con stenosis mitral, 3 con stenosis pulmonar, e 1 con hypertension pulmonar. In omne le 10 il habeva isolate hy-

pe rophia dextero-ventricular, e in omnes pr funde undas S esseva presente in V_1, V_2, o 3.

roportiones R/S de minus que 1,0 in V_1 es va presente in 3 casos. Le voltage de R in V_1 esseva infra 0,5 millivolt in 3 casos. U las R in aV_R esseva absente in 3 casos.

.e vectocardiogrammas de iste patientie in icava hypertrophia dextero-ventricular e ill strava le rationes pro le constatationes ele trocardiographic.

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Heinz, R., and Hultgren, H.: Atrial Fibrillation Following Mitral Valvulotomy. Arch. Int. Med. **99**: 896 (June), 1957.

Atrial fibrillation appeared following mitral valvulotomy in 47 per cent of 77 patients who had a normal sinus rhythm prior to surgery. Fibrillation appeared most frequently on the second postoperative day and rarely on the day of surgery. Spontaneous resumption of sinus rhythm occurred in 10 patients, and quinidine restored sinus rhythm in 16 patients, leaving 10 who had persistent postoperative atrial fibrillation. Since the ventricular rate is high in patients not receiving digitalis, and since additional digitalis was needed to slow the ventricular rate of most patients who developed postoperative atrial fibrillation, all patients should probably be fully digitalized prior to valvulotomy. Since spontaneous resumption of sinus rhythm occurs in many patients, quinidine may be withheld until the seventh postoperative day. It also may be more effective at that time, since factors responsible for the onset of atrial fibrillation have by then apparently diminished.

Simon

Perforation of the Heart during Cardiac Catheterization and Selective Angiocardiography

By Doris J. W. Escher, M.D., Jerome H. Shapiro, M.D., Berta M. Rubinstein, M.D., Elliott S. Hurwitt, M.D., and Sidney P. Schwartz, M.D.

Perforation of the myocardium is rare during cardiac catheterization. The precautions to be exercised, particularly in regard to clinical management, are delineated in this communication.

PERFORATION of the heart during the course of cardiac catheterization or selective angiocardiography is a rarity.[1] This case is reported as a reminder of its possible occurrence and to describe the roentgen findings that established the correct diagnosis.

Case Report

The patient, a 24-year-old woman, was admitted to Montefiore Hospital on January 10, 1958, for evaluation of suspected congenital heart disease. She gave a history of uncomplicated scarlet fever at the age of 2 years. Childhood activity was unlimited but undue fatigability was present. A heart murmur had been present since 1951. In the past 2 years there was an increase in weakness and the onset of exertional dyspnea. In the past year there were also several episodes, apparently syncopal in nature, of transient loss of consciousness and spontaneous recovery.

Physical examination showed a normal, symmetrical, clear chest. The blood pressure was 125/60, the pulse was 100, and the respirations were 20. The point of maximal cardiac impulse was in the fifth intercostal space in the anterior axillary line. The rhythm was regular. There was a long, rough systolic murmur and thrill along the left sternal border. Both were maximal at the third intercostal space. The pulmonic second sound was equal to or slightly louder than the aortic second sound. The arterial pulsations in the neck were active but not suggestive of aortic insufficiency. There was no venous distention. Peripheral arterial pulses were normal. On January 11, 1958, an electrocardiogram was interpreted as showing combined ventricular hypertrophy. Chest roentgenograms with barium swallow demonstrated mild prominence of the pulmonary artery segment with slight enlargement of the left atrium (fig. 1). The admission diagnosis was interventricular septal defect.

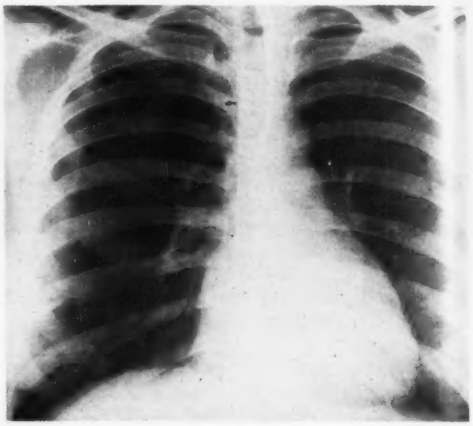

Fig. 1. Posteroanterior chest roentgenogram with barium swallow. Pulmonary artery segment somewhat enlarged.

On January 15, 1958, commencing at 1.30 p.m. the patient underwent a standard diagnostic cardiac catheterization. She was postprandial, sedated by 100 mg. of sodium barbital, and breathing room air. A no. 8, 125-cm. Cournand catheter was passed without difficulty via the left brachial vein into the right heart and out to the pulmonary arteries. Sequential sampling of blood for oxygen saturation and pressure tracings was done during the advance and withdrawal of the catheter.

The data failed to confirm the clinical impression of an intracardiac shunt but p-

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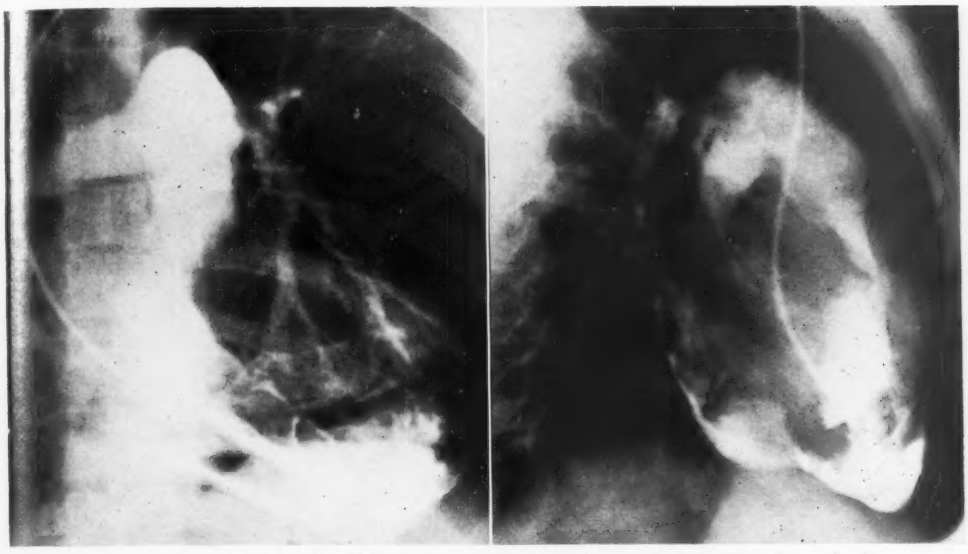

FIG. 2. Selective angiocardiography. Anteroposterior and left lateral projections obtained 2 seconds after injection of opaque medium. Tip of catheter is located at apex of right ventricle directed toward left, caudally and anteriorly. A small quantity of opaque material is in pericardial cavity along the diaphragmatic surface. Lateral projection, in addition, shows opaque medium in pericardial cavity extending upward, anterior, and posterior to heart. Intracardiac opacification delineates mild infundibular stenosis.

peared to have demonstrated, instead, an apparently isolated infundibular pulmonic stenosis, with the systolic pressure in the right ventricular inflow at 55 mm. Hg and in the infundibulum and pulmonary artery at 15 mm. Hg.

The cardiac catheterization was completed by 3 p.m. A selective intracardiac biplane angiocardiogram was then performed. The Cournand catheter was withdrawn and replaced by a no. 7 National Institutes of Health (NIH) catheter. The tip was positioned near the apex of the right ventricle and the position was confirmed by fluoroscopy, right ventricular blood oxygen, and pressure determinations. The patient's arms were then placed in full extension above the head to clear the chest for the lateral projection of the angiocardiogram. To minimize the effect of the catheter tip retraction, which commonly occurs with the repositioning (due to the lengthening of the venous channel with the conversion of partial extension of the arm to full extension) and to avoid displacement back into the right atrium, the catheter was advanced slightly as the left arm was moved. The patient was then moved along the fluoroscopic table to a biplane Schonander serial-film changer. The catheter was again secured by a slight forward thrust. Scout roentgenograms at 3:30 p.m., though showing the catheter to be slightly deeper in the apex than earlier, gave no cause for concern. Throughout this period the electrocardiogram, heart rate, and right ventricular pressure curve showed no irregularities or variations. The rather low arterial blood pressure (85 mm. Hg systolic) was thought to be due to needle damping and not to physiologic depression. At 3:45 p.m. intravenous sodium pentobarbital sedation 0.2 per cent in 5 per cent glucose was started. During a 1-hour technical delay that followed, the patient's condition seemed to be stable, though it was noted that she seemed to be quite pale. At 4:15 p.m., with the patient still sedated and breathing 100 per cent oxygen by mask, 50 ml. of 70 per cent Urokon was injected into the right ventricle by a Gidlund pressure syringe at a pressure of 7 Kg. per cm.^{2} The sequence of roentgen exposures

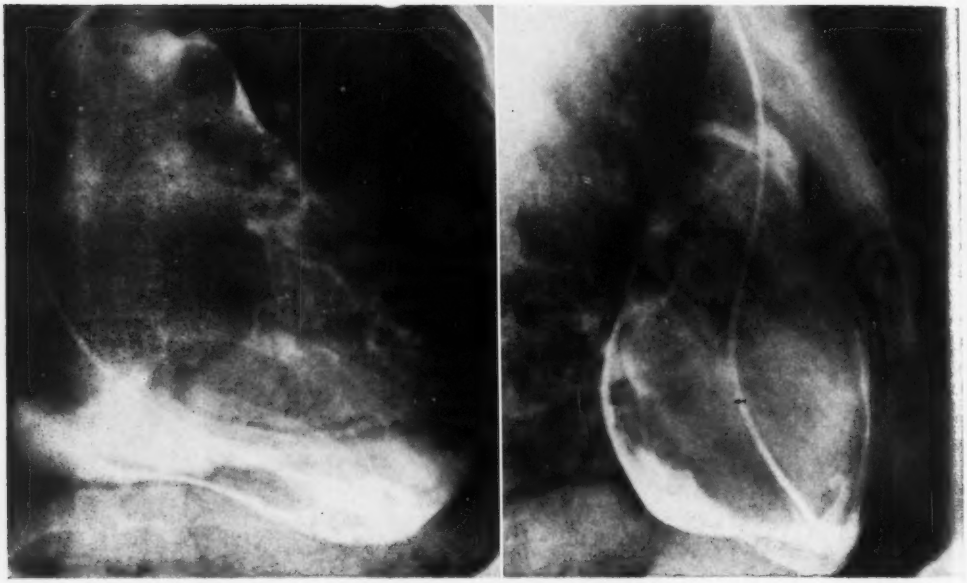

FIG. 3. Selective angiocardiography. Anteroposterior and left lateral projections obtained 8 seconds after injection of opaque medium. There is increase in quantity of opaque material, which now completely outlines the extent of the pericardial cavity. At base of heart, opaque material outlines aorta and pulmonary artery. Radiolucent defect in diaphragmatic portion of pericardial cavity indicates presence of blood. Several globules of opaque medium in apex of right ventricle may mark site of perforation.

was 6 per second for 2½ seconds followed by 3 films every 2 seconds for an additional 12 seconds. Sodium pentobarbital was then discontinued and by 4:45 p.m. the patient returned to the recovery room, still asleep. The pulse was 95 to 105, unchanged since the start of the procedure. The systolic blood pressure was 130 mm. Hg.

The roentgenograms were immediately processed and studied. Coincident with the anticipated appearance of contrast medium within the right ventricle, some was seen in the pericardial cavity, the amount gradually increasing to the end of the examination (figs. 2 and 3). Several globules of opaque medium were seen in the right ventricular apical myocardium distal to the tip of the cardiac catheter, suggesting that perforation of the heart had occurred at this point. With the implied potential of cardiac tamponade, a constant check of pulse and blood pressure was begun, the surgical service was notified, blood was ordered and protamine sulfate was given to counteract any residual heparin activity from the cardiac catheterization. At 5:10 p.m. a portable chest x-ray in the sitting position showed the cardiovascular silhouette to be somewhat enlarged with opaque medium collected along the diaphragmatic surface of the pericardial cavity (fig. 4). An electrocardiogram showed no change when compared with the admission study.

Following this, though the patient awakened, the heart rate rose to 139, the blood pressure dropped to 70/40 mm. Hg and the development of cardiac tamponade seemed certain.

At 6:30 p.m. the patient was transferred to the operating room, where, under general endotracheal anesthesia, the right chest was opened and the heart was exposed. The pericardium was seen to be tensely distended and deep blue in color, and the cardiac pulsations were extremely feeble. A vertical pericardial incision was made anterior to the right phrenic nerve and blood stained fluid, estimated to be

200 ml. in volume, gushed forth under tremendous pressure. The heart beat immediately became strong and full and the peripheral pulses returned.

At surgery the right atrium was quite large. The heart was rotated so that the apex, which consisted mainly of right ventricle, was positioned anteriorly and far to the left. At the apex of the right ventricle, there was a soft cleft, the point where the perforation must have occurred. There was no further bleeding. The pericardium was irrigated with large amounts of saline solution. No thrills were felt anywhere over the heart. However, direct pressure tracings confirmed the presence of a ventricular-pulmonary gradient. The condition of the patient at the end of the operation was good.

The postoperative course was not eventful and the patient was discharged from the hospital on January 25, 1958.

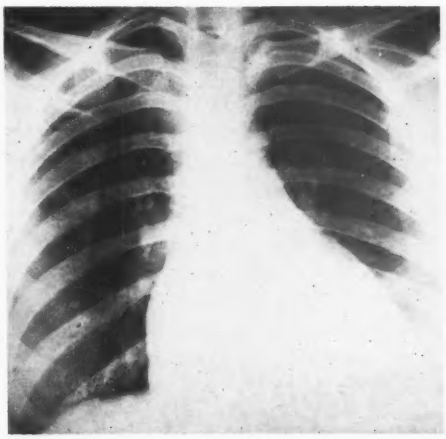

FIG. 4. Portable roentgenogram of chest in sitting position. Despite difference in technic, heart is enlarged when compared with the admission study (fig. 1). Opaque medium present in pericardial cavity, particularly along diaphragmatic surface.

DISCUSSION

Selective angiocardiography is now a preferred technic for evaluation of many forms of heart disease. A Cournand-type catheter with a single opening at the tip is used for the physiologic exploration during cardiac catheterization. With pressure injection of contrast medium through this catheter, there is a recoil effect that displaces the catheter tip. Its relatively thick wall and narrow bore slow the speed of injection. The NIH catheter, designed for selective angiocardiography, has a thinner wall than the Cournand catheter of the same external gage, has a greater luminal diameter, a closed tip, and discharges through 4 spirally placed side holes 1 to 2 centimeters proximal to the tip. It permits injection of a larger volume of opaque medium per second without increase of injection pressure, discharges the opaque medium over a wider area more rapidly, and eliminates the recoil effect. However, with the NIH catheter, it is possible for the tip to penetrate the myocardium for as much as 1 cm. with normal blood pressure and blood sampling still obtained through nonocceluded proximal side orifices. It is similarly possible, for the same reason, that test doses of opaque medium, normally injected at relatively low pressures, may fail to demonstrate the occurrence of such accidents when the opaque medium exits from the same proximal nonocceluded openings. If some of the side-wall openings have also penetrated the myocardium, an accentuation of a perforation may result with a pressure injection. This type of accident is less probable with a Cournand catheter, as damping of the pressure-tracing occlusion of its single-tip orifice against the endocardium signals its malposition. The very real roentgen advantages of the NIH catheter over the Cournand catheter in selective angiocardiography, however, justify the risk of its use.

In this case, there is reason to suspect that perforation probably did not occur with the Cournand catheter, which is relatively flexible and which was not inserted in the area of the apex of the right ventricle. The perforation occurred more likely during the insertion of the relatively sharp tipped, more rigid, NIH catheter, most probably when the catheter was additionally advanced after its initial positioning. If this is true, then myocardial penetration must have occurred without the patient's cardiac pulse, respirations, blood pressure, electrocardiogram, or general status showing any evidence thereof. It is not clear,

either, whether the side orifices of the catheter participated in widening the perforation or whether the opaque medium was forced out during the brief period of increased right ventricular pressure that accompanied the sudden augmentation of volume by rapid injection. True clinical tamponade was not seen until 2½ hours after the catheterization, 1¾ hours after the catheter replacement, and 1 hour after the angiocardiogram. There is also reason to wonder, in view of past experience, whether this perforation could occur in a normal myocardium. Indeed, while most perforations of the normal heart may be expected to seal spontaneously, in this case it was the unpredictability of a congenitally abnormal heart, with a myocardium soft enough to be ruptured by a catheter, that encouraged surgery as the treatment of choice. Consideration was also given to the possibility of irritation of the pericardial surface by the mixture of Urokon and blood, although there is no available evidence that Urokon will act as an irritant to serosal surfaces. Needle aspiration of the pericardium, transfusion, and a trial of waiting are the considered alternate therapeutic approach.

The diagnosis of perforation of the heart on the plain roentgenograms of the chest is based upon the accumulation of blood within the pericardial cavity. As the volume of fluid within the pericardial cavity needed to increase the area of the cardiac silhouette roentgenographically is almost equal to the amount of fluid found in cases of acute cardiac tamponade, this method of diagnosis is fraught with delay and limitations. It is generally thought that at least 200 ml. of fluid must be present in the pericardial cavity before the diagnosis of pericardial fluid is roentgenographically feasible. Davis[2] reports that 300 ml. or more are usually found in patients with acute fatal tamponade.

This case is a direct angiocardiographic demonstration of a perforation of the right ventricle as indicated by the presence of a small amount of opaque medium dispersed within the pericardial cavity. The opaque medium was observed in the beginning of the angiogram opposite the tip of the catheter in the pericardial cavity outlining the diaphragmatic surface of the heart and later outlining the extent of the pericardial cavity including its limits at the base of the heart. The radiolucent defects noted in the pericardial cavity indicate the presence of blood. The preponderant volume of opaque medium within the cavity of the right ventricle suggests that the perforation was quite small and that most or all of the holes near the tip of the catheter were lying within the cavity of the right ventricle. If the perforation had not been demonstrated directly by angiography, its existence in the presence of clinical symptoms might have been suspected by an increase in the thickness of the lateral cardiac walls due to the hemopericardium.

Summary

The occurrence of this case of perforation of the myocardium during cardiac catheterization with selective angiocardiography serves to emphasize some of the risks taken in the application of several of the newer, specialized methods now available for the evaluation of congenital heart disease. With careful technic and good teamwork, however, the danger to the patient can be held to a minimal level and is far outweighed by the positive values of the procedures.

Summario in Interlingua

Le facto del occurrentia de iste caso de perforation del myocardio durante catheterisation cardiac con angiocardiographia selective servi a relevar certes del riscos que es inherente in le uso de plures del nove e specialisate methodos nunc disponibile pro le evalutation de congenite morbo cardiac. Tamen, le plus meticulose attention technic e alte grados de cooperativitate del participantes reduce le risco pro le patiente a un mesura minimal e es plus que compensate per le valor del manovra.

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CLINICAL CONFERENCE

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Cor Pulmonale in a Case of Interstitial Fibrosis of the Lungs with Death in a Sickle-Cell Crisis

By WALTON R. AKENHEAD, M.D., RONALD A. WELSH, M.D., AND EDGAR HULL, M.D.

THE patient, a 30-year-old Negro laborer, was referred to the Charity Hospital Outpatient Clinic in December 1952 with a history of shortness of breath that had been progressive since its onset, approximately 2 years previously. Mild cough productive of small amounts of white sputum had been present for several months. There had been no chest pain, fever, hemoptysis, or pedal edema. There was no history of heart disease, rheumatic fever, syphilis or exposure to noxious agents. His work in a sugar refinery did not expose him to bagasse dust. Physical examination was recorded as essentially negative except for slight increase in pulse and respiratory rates. Initial laboratory work showed the following: Hemoglobin 12 Gm., red blood cell count 4.2 million, white blood cell count 22,760 with a normal differential count. There was less than 5 per cent sickling in 24 hours. No acid fast bacilli were noted on direct smear of the sputum. An electrocardiogram was normal. Digitalis therapy over the next several weeks gave no improvement.

He was admitted to a Veterans Hospital in February 1953 and 8 weeks later was transferred to Charity Hospital for further study. Additional history revealed jaundice of unknown duration at the age of 12 and "rheumatism and tonsillitis" at the age of 13. He was febrile during the latter illness and remained in bed for about 3 months.

Physical examination in April 1953 revealed a well developed and nourished Negro who did not appear particularly ill. Blood pressure was 124/76, pulse 88 per minute, temperature 98.6 F., ventilatory rate 24 per minute. Aside from a soft apical systolic murmur the physical examination was normal. Venous pressure was 140 mm. of water. Circulation time (arm to tongue) was 25 seconds. Routine hemogram was essentially normal except for mild leukocytosis. X-ray of the chest revealed prominence of the pulmonary conus with a heart of normal size. Fluoroscopy gave the impression of a prominent, actively pulsating pulmonary artery with slight prominence of the right ventricle. An electrocardiogram was within normal limits but there had been definite shift of the QRS axis toward the right as compared to the record of December 1952 (fig. 1*A* and *B*). Muscle biopsy was normal.

The patient was hospitalized several times during the next few months. His dyspnea was becoming more severe and was not responsive to digitalis, bronchodilators, or steroids.

Pertinent aspects of the pulmonary function studies were as follows:

	Vital capacity	*Maximum breathing capacity*	*Resting minute ventilation*
April 27, 1953.....	2630	92.9	12.11
June 9, 1953.....	1825	80.2	14.88
June 18, 1953.....	2280	112.0	14.00
July 7, 1953.....	2240	100.0	18.62
Sept. 8, 1953.....	2430	99.0	22.7

	Air		*Oxygen*	
Arterial Oxygen	*Rest*	*Exercise*	*Rest*	*Exercise*
April 22, 1953...	80%	74%	99±%	99±%
June 10, 1953....	79%	82%	98%	99+%
July 10, 1953....	72%	61%	93%	76%

From the Charity Hospital of Louisiana at New Orleans and the Louisiana State University School of Medicine, Departments of Medicine and Pathology, New Orleans, La.

Cardiac catheterization showed pulmonary hypertension (75/35) with no evidence of left-to-right shunt.

Numerous routine laboratory determinations showed no abnormalities except for a rather persistent mild leukocytosis. No sickle-cell preparations were done except the one done upon his initial admission to the Outpatient Clinic. Many target cells were noted in one smear. Electrocardiograms taken in August and September 1953 showed progression of QRS axis deviation to the right with the R waves in V_1, V_2, V_3 becoming higher.

He entered the hospital on his final admission, September 29, 1953, complaining of dyspnea, mild lower right chest pain, severe cramping pain in the legs and arms, and a transient episode of syncope. Physical examination revealed a blood pressure of 114/92, pulse 144, respiratory rate 34. Mucous membranes were cyanotic. A harsh systolic murmur at the mitral area was heard. The heart was not clinically enlarged. The lungs were clear. Blood calcium was 11.5 mg. per cent and serum bilirubin was 4.5 mg. per 100 ml. (direct 1.6, indirect 2.9).

The patient died several hours after admission.

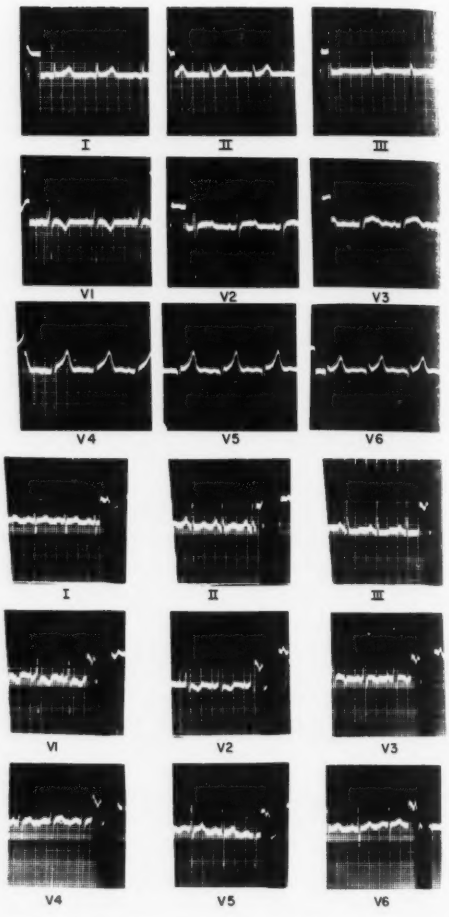

FIG. 1 *Top.* Electrocardiogram taken in December 1952. *Bottom.* Electrocardiogram taken in July 1953 showing shift of QRS axis to the right and increased amplitude of the R waves in $V_{1, 2, 3}$.

DR. WALTON R. AKENHEAD: This man's illness apparently lasted about 1½ years and initially featured increasing dyspnea subsequently attended by evidence of right ventricular hypertrophy and arterial oxygen unsaturation and finally ended in an episode characterized by jaundice and pain in the chest, arms and legs.

Since this patient's initial clinical manifestation was shortness of breath unattended by evidence of cardiac disease or severe anemia, it seems clear that his dyspnea was pulmonary in origin, with the pathologic process involving the lung parenchyma or pulmonary vasculature or both.

The pulmonary function studies show reduction in both vital capacity and maximum breathing capacity but only slightly so, and certainly not to the degree expected in gross ventilatory dysfunction. The arterial oxygen saturation studies though not uniform do show progression to the point where there is diminished arterial oxygen saturation with exercise when the patient breathed air or 100 per cent oxygen. These findings tend to place the difficulty in the category of a right-to-left shunt or a severe defect in gas diffusion or block at the alveolar capillary membrane.

Cardiac catheterization revealed the presence of definite pulmonary hypertension and failed to show any evidence of atrial or ve

ticular septal defect. The several electrocardiograms showed steady progression from a normal tracing to one consistent with right ventricular hypertrophy. This finding would suggest and fortify the impression that this patient's cardiac involvement is secondary to the pulmonary hypertension.

If we are agreed that this patient had some sort of rapidly progressive pulmonary or pulmonary vascular disease leading to arterial oxygen unsaturation, cor pulmonale, and death, then we may discuss some of the diagnostic possibilities.

Perhaps the most common lung condition leading to cor pulmonale is emphysema. It is the time-honored concept that pulmonary hypertension is secondary to the increased resistance resulting from the reduction in capillary bed occasioned by the breakdown of alveolar septa. There is much thought and some evidence at present that this explanation is far too simple. It seems more likely that some complex mechanism involving communication between the low-pressure pulmonary vascular system and the high-pressure bronchial vascular system may be at fault. In this case the relatively normal maximum breathing capacity and the diminution of oxygen saturation during exercise would rule out obstructive emphysema as the cause of this patient's pulmonary hypertension. In emphysema the maximum breathing capacity is reduced out of proportion to the vital capacity because of expiratory "air trapping" when the patient attempts rapid, deep breathing. In the usual case of emphysema with oxygen unsaturation, exercise results in better ventilation and distribution of air and oxygen, with some rise in oxygen saturation of the arterial blood. It would be distinctly unusual for emphysema to begin so abruptly and terminate so rapidly in a person of this age without obvious bronchial disease. Moreover, emphysema is not a common disorder in the Negro.

We are becoming more aware of sickle-cell disease as a cause of pulmonary hypertension with eventual cor pulmonale. The basic defect in sickle-cell disease is the abnormal architecture of the hemoglobin molecule. This readily explains the abnormal shape of the cells which, together with the tendency of these cells to stagnate, conglutinate, and thrombose in small vessels, is the key to the pathology of the disease. It has long been recognized that patients with sickle-cell states are prone to thrombosis. The frequent occurrence of splenic and cerebral infarction and the common ischemic leg ulcers are clinical and pathologic events that attest to the thrombotic propensity of these patients. It has also been long recognized that low oxygen tension is the most powerful of the "sickling potentiators." Patients with sickle-cell disease show 3 or 4 times more "sickling" in venous blood than in blood from the arterial side of the greater circulation. Individuals exhibiting the heterozygous sickle trait are prone to "thrombotic crises" when at high altitudes in an atmosphere of low oxygen tension. In view of the above observations it would follow that one could expect small vessel thrombosis in the lungs where oxygen tensions are low and flow is comparatively slow. This tendency would be increased should blood be flowing through poorly aerated areas of the lung. How much reduction of the capillary bed of the lung by repeated small infarctions is necessary for production of pulmonary hypertension and cor pulmonale is not known but judging on clinical grounds alone the amount of pulmonary involvement required to compromise the pulmonary circulation must be considerable. However, should an oxygen diffusion defect occur as a consequence of widespread fibrosis due to repeated small, subclinical infarctions, arterial hypoxia might contribute to the development of pulmonary hypertension. With the better methods of identification of the various combinations of abnormal hemoglobin values that comprise sickle-cell disease and its variants it is more than likely that many cases of pulmonary hypertension heretofore regarded as "primary" will be ascribed to repeated small pulmonary infarctions. The more judicious

use of transfusions and the better armamentarium against infections will no doubt allow many of these patients afflicted with abnormal hemoglobins to live sufficiently long to manifest the ultimate result of these pulmonary infarctions.

In this case it is unfortunate that more definitive studies relating to hemoglobin structure were not done. The demonstration of "less than 5 per cent sickling" and target cells in the absence of anemia, jaundice, or other hallmark of sickle-cell disease would lead one to believe that this patient had one of the heterozygous sickle-cell variants rather than the homozygous sickle-cell disease. However, it should be mentioned that occasionally one may see the first clinical manifestations of the homozygous sickle-cell state in well developed, apparently healthy Negro adults with no history or evidence of anemia, jaundice, hemolytic crisis, leg ulcers, skeletal abnormalities, or other hallmarks of the disease that are usual from childhood in the classic case of sickle-cell disease.

The final episode of the patient's illness is worthy of some comment. In addition to his increasing dyspnea, the patient had an episode of syncope and complained of right lower chest pain and severe cramping pain of the arms and legs. Jaundice was noted for the first time. This type of exitus may be seen in patients with sickle-cell disease as a result of widespread conglutination of sickle cells with thrombosis, obstruction, or impairment of circulation with resultant infarction or ischemia. It is unfortunate that blood studies were not done during the few hours of his last hospitalization. It is inviting to speculate that his increasing arterial and venous oxygen unsaturation may have potentiated his "sickling" tendency.

The diagnosis of periarteritis nodosa of the pulmonary arteries is suggested by the persistent leukocytosis and the rapid course of the disease. The absence of fever and the negative muscle biopsy militate against this diagnosis but do not in any way rule it out. A lung biopsy would be necessary to establish or thoroughly to negate such a diagnosis.

The opinion generally held by the staff who cared for this man was that his basic difficulty was interstitial fibrosis of the lungs of the variety described by Hamman and Rich. The rapidly progressive course with increasing dyspnea and cyanosis and eventual evidence of right ventricular hypertrophy is almost a carbon copy of the cases originally described by Hamman and Rich. In the usual case of interstitial fibrosis with alveolar capillary diffusion block the already reduced arterial oxygen saturation during the breathing of air will further diminish with exercise, but the breathing of 100 per cent oxygen will usually result in complete saturation at rest and after exercise. In this case this was essentially true when studies were done early in his hospitalization. Later on, studies showed that arterial oxygen unsaturation was present at rest, breathing air or oxygen, and that this unsaturation was increased by exercise whether the patient was breathing air or oxygen. In this regard the findings are those of a right-to-left shunt. This is not altogether surprising, since it seems reasonable that if the alveolar-capillary interface is sufficiently thickened the diffusion of oxygen into capillaries will be so seriously compromised that the existence of blood flow in areas so involved will, in essence, be a right-to-left shunt.

DR. RONALD A. WELSH: The significant findings at necropsy were limited to the lungs, heart, and spleen. There were diffuse fibrous adhesions in both thoracic cavities. Both lungs were essentially similar in gross appearance, firm in consistency throughout all lobes. The cut sections demonstrated a diffuse coarsening of lung architecture with no evidence of gross hemorrhage, edema, or consolidation. The hilar lymph nodes were not significantly enlarged. The right ventricle of the heart was hypertrophied and dilated. An unexpected finding was an extremely small fibrotic spleen, weighing only 14 Gm. The remainder of the organs were essentially normal on gross examination.

Microscopic examination of the lungs revealed diffuse interstitial fibrosis of a type

similar to that described by Hamman and Rich (fig. 2). The alveolar walls were thickened and contained an increased amount of collagen along with an apparent increase in capillaries. There were small numbers of lymphocytes and occasional plasma cells in the interstitial tissue. The alveolar spaces were almost uniformly lined by cuboidal cells, and contained variable numbers of histiocytes and occasional red blood cells. There were patchy areas of compressed and collapsed alveoli with adjacent areas of dilated emphysematous spaces. The red blood cells showed marked sickling in the vessels of the lung, as well as in all organs examined. Although no definite recent thrombi could be demonstrated, several pulmonary arteries were found showing old, recanalized thromboses (fig. 3). The splenic pulp was completely replaced by fibrous tissue containing large masses of calcium and hemosiderin. A section of bone marrow was hyperplastic, with an increased erythroid component.

This case presents several interesting features for pathologic correlation. First, the arterial oxygen studies initially were consistent with an alveolar gas diffusion block, but in the later studies there was a change with evidence pointing to a right-to-left shunt in the pulmonary circulation. In examining these lungs microscopically, one is struck by the marked over-all vascularity in the individual alveolar walls. This feature of pulmonary "angiosis" in the Hamman-Rich syndrome has been pointed out by Golden and Bronk,[2] and it appears that in this case in many areas there has been a definite increase in capillaries in the alveolar walls. Although an actual gross right-to-left shunt has not been accurately identified in this case, there is definite anatomic evidence of an abnormal vascular pattern, and injection studies in future cases may shed light on the exact nature of the vascular cross connection suspected physiologically by Dr. Alpenhead in the studies of arterial oxygen saturation.

This case is complicated by the associated

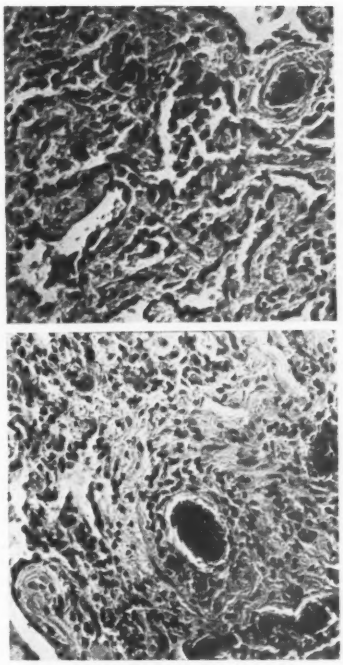

FIG. 2 *Top.* Photomicrograph showing diffuse interstitial fibrosis of lung.

FIG. 3 *Bottom.* Photomicrograph of recanalized thrombosed pulmonary artery.

clinical evidence of a terminal hemolytic disease, which is accompanied by pathologic evidence of normoblastic hyperplastia of the bone marrow, pronounced sickling of the erythrocytes, and a shriveled, fibrotic spleen. I am interested in the original sickling preparation reported on this patient as 5 per cent sickled cells present. Certainly in the autopsy tissues there is more than 95 per cent sickling seen. It is probable that the original preparation did not reproduce the severe oxygen deprivation seen in the tissue, or the original preparation may have been examined too early. In our experience, a shrunken fibrotic spleen such as in this case is ordinarily seen in true sickle-cell disease of homozygous "S"-hemoglobin type. When changes in the size of the spleen occur in the heterozygous "S"-hemoglobin individuals, there is usually splenomegaly, although it is probable that future anatomic studies of

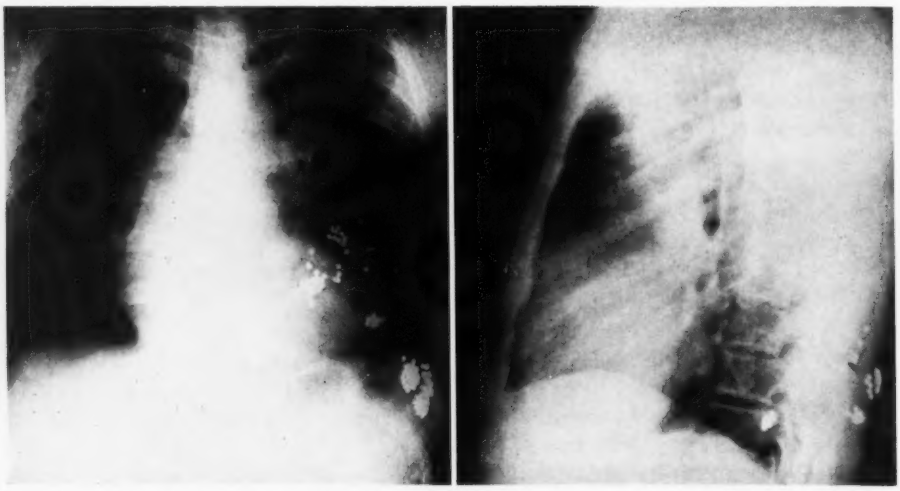

FIG. 4 *Left.* Posteroanterior view of chest showing the prominent pulmonary artery. *Right.* Lateral view of chest showing contour consistent with right ventricular hypertrophy.

large groups of individuals with heterozygous sickle-cell hemoglobin will disclose rare instances of a similar, severe, splenic atrophy.

The sickle-cell disease is most likely a coincidental associated disease, and to my knowledge does not produce diffuse interstitial fibrosis of the lungs of the Hamman-Rich type. The recanalized thrombi in the pulmonary arteries may represent the effect of previous sickle-cell crises and may contribute to the cor pulmonale. Examination of reported cases of Hamman-Rich syndrome reveals no significant association with sickle-cell disease; actually the syndrome has been found in about equal proportions in the white and Negro races. Sickle-cell disease was undoubtedly a potent contributary factor in this patient's demise, particularly in view of the hemolytic crisis that was observed clinically.

The pathologic diagnoses were diffuse interstitial fibrosis of the lungs (etiology unknown); hypertrophy of the right ventricle; sickle-cell disease, —normoblastic hyperplasia of the bone marrow, and atrophy of the spleen.

DR. EDGAR HULL: I first saw this patient at a clinical conference in April 1953, and my recorded opinion was that he had "diffuse interstitial fibrosis of the lungs." I did not consider the possibility of a sickling state as a factor in his illness, either then or on the 2 or 3 other occasions when I saw him or discussed his case. Probably because he was never anemic and because of the single negative sickle preparation, none of the others who followed his course mentioned the sickle state as a possible factor in the pathogenesis of his pulmonary hypertension, although we knew that pulmonary hypertension and cor pulmonale are common enough in sickle-cell disease. We have been aware of this complication since the report of Yater and Hansmann in 1936,[3] and we recognize that some of the unusual murmurs (particularly the very loud systolic murmurs and the occasional diastolic murmurs heard to the left of the upper sternum) are due to dilatation of the pulmonary artery. We frequently recognize pulmonary infarction in patients with sickle-cell disease; even in the absence of "clinical" signs of pulmonary disease transient densities are often seen in the chest x-rays of these patients.

I recall that during the admission of July 1953, when the arterial oxygen saturation of this patient failed even to approach 100 per cent while breathing oxygen, there was spec-

u tion that he must have, in addition to the p mary pulmonary disease, an anatomic p ency of the foramen ovale, through which r ht-to-left shunting occurred as right ventr ular failure developed and right atrial p ssure increased. Like Dr. Akenhead, I th ught that the "shunt" bypassed the air in th alveoli, but not necessarily the lungs—th t it was probably intrapulmonary.

Dr. Welsh has told us that in this case the si kle state was probably not concerned in th pathogenesis of the pulmonary fibrosis, bu that it was undoubtedly an important factor in his death. This opinion I accept, particularly since in part it substantiates our clinical diagnosis though it does not lessen our chagrin over missing half of the boat.

I wonder, however, whether the fibrosis may have been related to repeated subclinical episodes of small vessel, perhaps capillary, thrombosis, occurring over the years. This man may have been a heterozygous sickler, yet his spleen was as small and fibrotic as that of any S-S sickler. Indeed, Moser and Shea[4] have reported pulmonary hypertension and cor pulmonale in heterozygous sickle states.

Further and finally, at this time we have in the hospital a Negro man, age 52, whose illness, to use Dr. Akenhead's words, is almost a carbon copy of that in the case under discussion. He has been short of breath on exertion for about 7 months; on 2 occasions he has fainted during exertion. He has a big right ventricle (fig. 4*A* and *B*); electrocardiographic signs of right ventricular hypertrophy (fig. 5); signs of an oxygen diffusion defect without great reduction in maximal breathing capacity. He is not anemic (hematocrit 49 per cent); his sickle test is positive; electrophoretically he is heterozygous A-S. Is he, too, a case of the Hamman-Rich syndrome, or is his cor pulmonale due solely to the consequences of the sickle state?

DR. WELSH: The possibility that the entire clinical picture can be ascribed to sickle-cell disease alone is tempting to consider; however, I would like to clarify further that the old pulmonary thromboses in this case were too few in number to have resulted in such a degree of interstitial fibrosis. Likewise, if tiny capillary thrombi were a mechanism, as postulated by Dr. Hull, again we would expect to see diffuse interstitial fibrosis of this type in a higher frequency in the Negro race with sickle-cell disease, but apparently this is not the case.

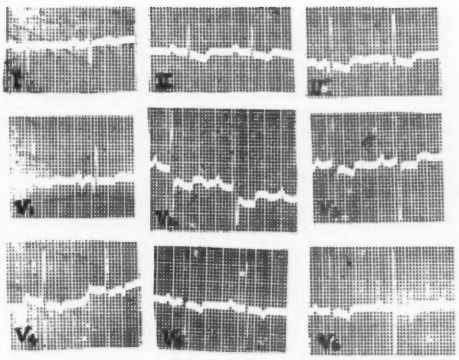

FIG. 5. Electrocardiogram showing signs consistent with right ventricular hypertrophy.

DR. AKENHEAD: In conclusion, we have presented a patient with diffuse interstitial fibrosis of the lungs with eventual development of pulmonary hypertension and cor pulmonale whose exitus was attended by a "sickle-cell crisis."

The altered cardiopulmonary physiology occasioned by the pulmonary pathology and the possible relationship between the hemoglobinopathy and the pulmonary fibrosis have been discussed. I suspect, as is usual in these sessions, that we have raised more questions than we have settled.

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CLINICAL PROGRESS

Symposium

Unsettled Clinical Questions in the Management of Cardiovascular Disease

Guest Editor: LOUIS N. KATZ, M.D.

A panel discussion on unsettled clinical questions in the management of cardiovascular disease was conducted at the Thirtieth Scientific Sessions of the American Heart Association held at the Sherman Hotel, Chicago, Friday afternoon, October 25, 1957. The panel was comprised of the following members: LOUIS N. KATZ, *Chicago, Ill.*, MODERATOR; GEORGE E. BURCH, *New Orleans, La.*; ALBERT DORFMAN, *Chicago, Ill.*; A. CARLTON ERNSTENE, *Cleveland, Ohio*; HANS H. HECHT, *Salt Lake City, Utah*; and ROBERT L. PARKER, *Rochester, Minn.*

MODERATOR KATZ: It is our plan in this panel to permit each of the panelists to speak uninterruptedly for a few minutes on one aspect of the subject. After each one has spoken, we will allow the members of the panel to question one another. Then if time permits, questions received from the floor will be answered.

Before I speak about the treatment of atherosclerosis, the subject I assigned to myself, I would like to say a few things about what is meant by an unsettled question. This is important, since the definition of a proposition determines the approach to it.

In the present era, we live in a fish bowl in medical research. New information is quickly picked up by the press, the lay magazines, the radio and television, and the general public is bombarded with uncritical reports of new discoveries in diagnoses and therapy. They in turn confront the doctor with this information, or misinformation, and expect him to be prepared to apply this widely advertised bit of so-called knowledge to themselves. Otherwise the physician takes the risk of being considered old fashioned and behind the times. Add to this, the constant bombardment of information—more mature, of course, but still sometimes out of context—of the mailed brochures, letters, and handouts of our pharmaceutical firms. Since sales are their legitimate goal, they stress new drugs. Is it any wonder that the physician has great difficulty in keeping his balance and in clearly differentiating that which is settled from that which is still unsettled?

Besides, much of our clinical literature is based on improperly designed scientific studies. Too often drugs and procedure are considered beneficial on the basis of poorly designed and somewhat uncritical observations. There is too much of the case-report approach to such observations. While the data may be true for that particular case or group of cases, they are not necessarily valid for all patients unless the data can be shown to be statistically valid. Statistical validity depends on proper design of the test, true randomness of selection of cases, a large enough case load, the use of matched controls, the employment of the proper placebo in them, the use of the "blind" or "double-blind" method of selection of cases and analysis of data, etc. By blind, I am of course referring to the proper care in keeping knowledge of the use of both placebo and drug from the patient and clinical observer of the patient. A concerted attempt to keep to a minimum the uncritical, poorly controlled and improperly conducted clinical studies would help not only in preventing the cluttering up of the literature but would be helpful in avoiding

many of the periodic transient fads that sweep the profession.

There is something wonderful about enthusiasm. It is contagious. When a young or old person makes a new discovery he is enthusiastic in his lectures and writings about it. This is proper. But the physician must be wary of such reports. He must constantly ask himself whether or not the question is really settled.

This appeal on my part for proper scientific proof of new clinical data, and for the need to discount enthusiastic protaganism—as well as excessive skepticism—is not out of place. However, it is fair to point out that I value the bedside manner and the proper use of ceremony. Any approach that makes the patient feel better and that is not harmful to him may, in certain circumstances, be justified. And this includes new unproved drugs and procedures. But, the physician must recognize that he is employing them merely as part of a ceremony!

This summer, at the Harvey Tercentenary in London, I heard Dodd tell about the dogmatism with which Harvey practiced medicine at St. Bartholomew's Hospital. While doubtlessly better than his colleagues, this scientist in research 300 years ago was empirical in his practice of medicine. This leads one to wonder what our descendants will think of our present practice of cardiovascular surgery and medicine! Are we as dogmatic today as our predecessors were just 50 years ago? How much in cardiology really is settled?

The physician must practice with the background of information available in his time. He is no god, who can unravel all the mysteries. He must therefore be ready to discard the old dogmas when they are proved false and accept new knowledge only when he is convinced that it is true. It is for this reason that the family physician and the internist have so important a place in medicine. New knowledge is being constantly advanced by the research physicians and scientists and this has to be assimilated into the practicing physician's fund of applicable facts beneficial to his patient.

Let us now turn to the question of atherosclerosis. I will not deal with the problem of the factors that make atherosclerosis clinically manifest or causes death, rather I wish to deal with the factors that lead to the underlying disease—so prevalent in this country. It is obvious that if we understand what causes atherosclerosis and can prevent its occurrence, there will be no clinical manifestations or deaths. Without the underlying atherosclerosis, there are no atherosclerotic sequelae!

Is this problem of atherosclerosis settled? Not entirely. I think it is clear that it is a disease—which can be treated—based on some disturbance in lipid metabolism.

Is the role of diet in atherosclerosis settled? Not yet. There are significant leads as to overweight, total calories, calories from fats, and the role of unsaturated fatty acids, proteins, carbohydrates, vitamins and other trace substances including minerals, but these are only leads to working hypotheses, not proved concepts.

In my own department at the Michael Reese Hospital, we believe the facts are sufficiently certain to warrant a modification of the diet in persons who have had a clinical episode, like a myocardial infarct, a cerebrovascular accident due to atherosclerosis—and not all such are on this basis—or who have hypertension, nephritis, diabetes mellitus, or xanthomatosis; who are overweight (in this country); or have a markedly elevated blood cholesterol—there is no need to explore their blood lipoproteins routinely. These are the high-risk male patients who have a 13-fold greater chance of developing a clinical coronary episode than the average male patient. Observations carried out at Framingham, Mass., in a prospective study showed that obesity, hypertension, and hypercholesterolemia definitely increased the 4-year incidence of coronary episodes when compared with the normal weight, normotensive age-matched individuals with a normal cholesterolemia. When 2 or all of these 3 parameters were above normal, the incidence increased 10 to 15 fold. It is our recommendation that obese people reduce, that all high-risk patients reduce the fat content in their diet so as to

yield about 25 per cent of their calories, that saturated fats be replaced to a large extent—within the above limits—by unsaturated fats high in essential fatty acids, that empty calories from alcohol and refined carbohydrates be kept low, that the use of lean meat, poultry, sea food, skimmed milk, cereal, fresh fruit, jellies and marmalade spreads be encouraged, and that flavoring come from "tenderizers" of meat, relishes, and spices.

This is our opinion. It is not universally accepted and so it is still an unsettled question. It needs still to be proved that a group on such a diet for a protracted period will have fewer clinical episodes and a lower mortality than those not on such a diet. This has not been tested adequately.

The same is true for the long-term anticoagulants. The best controlled study in this area is being carried out by the British Medical Research Council. Their data in a well-matched long-term study have been inconclusive to date. They cannot assert that long-term anticoagulants have reduced morbidity or mortality in patients with coronary disease. It is still an unsettled question.

Lipotropic agents have not been found to play a significant role in atherosclerosis as far as morbidity and mortality are concerned.

Nicotinic acid, in pharmacologic doses, has been found to be hypocholesterolemic but it has not yet been demonstrated that it is antiatherogenic clinically. This is also true for sitosterol, corn oil, safflower oil, and linoleic acid. In fact the beneficial effect of all hypocholesterolemic agents in atherosclerosis is still unsettled.

There is some evidence that hypotensive drugs given to hypertensive patients tend to lessen clinical manifestations of atherosclerosis; but this too is unsettled.

As far as emotional stress is concerned—or for that matter physical stress and exercise on atherosclerosis—all these are still unsettled questions.

What about the use of estrogens in young males after an infarct of the myocardium, which my own group has been testing since 1952, now in some 270 patients, in a controlled matched study? While the results look promising they are not statistically significant. This problem too is unsettled. We believe it will take us at least 2 more years before we will have sufficient data to apply statistical evaluation satisfactorily.

Thus, it is obvious that despite the great mass of literature the entire problem of the clinical management of the basic atherosclerotic process shows promise of future clinical application, but, for the moment, it is not settled.

Now I am going to call on Dr. Ernstene, who has agreed to cover the fields of cerebrovascular disease, ischemic heart disease, angina pectoris, in addition to the role of surgery in these areas.

Dr. A. Carlton Ernstene: With regard to cerebrovascular disease, it seems to me that the most important unsettled clinical question has to do with anticoagulant therapy of cerebrovascular accidents. What are the indications for employing anticoagulant drugs? Are they of value? For what length of time should they be continued if they are to be used at all?

At present there seems to be fairly general agreement that drugs of this type are indicated in patients who have suffered from cerebral embolism, except when the embolism has occurred as a complication of bacterial endocarditis. In cerebral embolism, however, the drugs are given not for a direct effect on the cerebral circulation but for the purpose of reducing the danger of further embolic accidents.

A number of cerebrovascular syndromes of thrombotic origin have been sufficiently well delineated to be recognized with accuracy. These include the syndromes of intermittent insufficiency of the basilar artery system, basilar artery thrombosis, and intermittent insufficiency of the carotid arterial system. These particular syndromes appear to be definite indications for the administration of anticoagulant drugs. The reports that have been published have been distinctly encouraging and certainly warrant further studies along the same line. But we do not know the actual value of the drugs and it has not been established whether they must be continued inde-

nitely in these cases or whether they can be discontinued after a certain length of time.

In the case of focal cerebrovascular disturbances the problem becomes even more difficult. Here there is so often the question of etiologic diagnosis. Frequently it is impossible to distinguish between cerebrovascular accidents that have resulted from hemorrhage and those that are due to thrombotic or nonthrombotic cerebral infarction. Whenever the possibility of hemorrhage cannot be excluded, anticoagulant drugs are contraindicated. Similarly, if it were possible to identify lesions resulting from nonthrombotic cerebral infarction, there would be no need for anticoagulant therapy. At the present time, focal cerebrovascular disturbances, whether repetitive in nature or isolated and including so-called "small strokes," probably should not be regarded as an indication for the administration of anticoagulant drugs.

The role of cerebral arteriospasm in causing cerebrovascular accidents and the extent to which the arteriospasm is influenced by sympathetic nerve influences remains a subject of heated neurologic debate. Pathologists have brought forward convincing evidence that nonthrombotic cerebral infarcts are far from uncommon. There appear to be only 2 possible explanations for these lesions. One is cerebral arteriospasm, and the other is that the infarcts result from a combination of cerebral arteriosclerosis and intermittent hypotension. Neurosurgeons have reported observing spasm of the superficial and penetrating arteries of the brain at the time of operation, and adherents of stellate ganglion block claim benefit in all types of nonhemorrhagic cerebrovascular accidents. Many neurologists and clinicians, however, remain completely skeptical about the occurrence of cerebral arteriospasm and the value of stellate ganglion block. On rare occasions a stellate block appears to bring about prompt improvement but whether or not this is fortuitous is an unsettled question. The procedure is safe and should have further and very critical study.

The management of angina pectoris presents many unsettled questions. The one of greatest interest has to do with the value of coronary vasodilator drugs other than nitroglycerin. The literature abounds with conflicting opinions, and I think it is safe to say that no one preparation thus far has been shown to be superior to all others. Furthermore, in the most carefully controlled studies it has not been possible to demonstrate a beneficial effect in a statistically significant number of cases. Nevertheless these preparations do at times seem to be of some help. I believe that those apparently beneficial effects are observed only in patients who have been fully instructed with regard to the importance of avoiding the various factors that may induce anginal attacks. Without attention to these restrictions there seldom is an appreciable reduction in the frequency or severity of the seizures. In the favorable cases, the effect of the drugs may be entirely psychologic, but the psychologic aspects of the management of angina pectoris are extremely important. To dismiss a patient with nitroglycerin as his only medication or to prescribe an additional preparation, which the patient recognizes as a sedative, may promptly convince him that his condition is hopeless. It appears justifiable, therefore, from the psychologic point of view alone, to give every patient who has angina pectoris a thorough trial of one or more of these preparations.

Opinions differ concerning the amount of exercise to be recommended for patients who are suffering from angina pectoris. Physicians who belong to the more orthodox school strongly recommend that the patient do his best at all times to keep his activity down below the point of bringing on an attack. On the other hand, several clinicians recommend deliberate walking on 4 or 5 occasions each day to the point of bringing on the first detectable symptoms of attack. It has been demonstrated in dogs with experimental coronary stenosis that exercise increases the rate of development of intercoronary collateral vessels. A similar effect in man might well be expected to improve the patient's exercise tolerance and possibly prolong his life.

Certain patients have coronary artery disease of such severity that in spite of all available measures of treatment they are unable to

carry out activities of any kind without experiencing angina pectoris. Formerly it was in these patients that surgical procedures such as paravertebral injection of alcohol or removal of the upper 4 or 5 thoracic sympathetic ganglia were employed. Today the surgical treatment of angina pectoris consists almost entirely of measures designed to improve coronary blood flow. I think it is perfectly fair to say that none of the operations thus far proposed has been proved to be of value. Evaluation of the procedures is difficult because the clinical course of angina pectoris varies within wide limits. Changes in the general health of the patient, seasonal changes in the weather, variations in the amount of stress in the person's life, and changes in the relative effectiveness of intercoronary collateral circulation all play a part in these fluctuations. In addition we must remember that patients with angina pectoris who are part of a series under study almost inevitably get better all-around care than the run-of-mill patient who has a similar problem. Furthermore, the enthusiasm of the surgeon and his medical colleagues is easily acquired by the patient. There can be no doubt about the importance of emotional factors in angina pectoris. The men who have been carrying on the developmental work in this field of surgery are to be commended and encouraged but until the operations have been shown to be of definite value by carefully controlled studies, they should not be recommended for widespread use.

In conclusion, just a word or two about essential hypertension. Reserpine, hydralazine, and the various ganglion-blocking agents are very helpful preparations. It remains doubtful, however, that their use is necessary in mild hypertension. Sedatives and correction of faulty living habits should be the first measures employed. In moderate or severe hypertension and in the malignant or accelerated phase on the other hand the use of antihypertensive preparations is indicated. It is often possible to reverse the malignant phase of hypertension and lengthen the life of the sufferer. The patients unfortunately usually remain far from well and die within a limited time of arteriosclerotic complications. These drugs are important, but the fact that they are available should not be allowed to interfere with basic research directed toward the primary cause or causes of essential hypertension.

MODERATOR KATZ: The next speaker will be Dr. Dorfman, who will talk about unsettled problems of rheumatic fever and rheumatic heart disease.

DR. ALBERT DORFMAN: In approaching problems of rheumatic fever and rheumatic heart disease, in the short time available, we might quickly consider various categories of problems. I should like to mention first questions of etiology, some of which are settled and some of which are unsettled.

We might emphasize one question that is, at least, consider settled—the fundamental etiology of rheumatic fever is related to an infection by Group A hemolytic streptococcus.

The unsettled parts of this problem are certain special characteristics of this reaction. We know little about why certain individuals develop rheumatic fever following streptococcus infections, and why certain age groups are particularly affected. We know little about why some individuals have a self-limited attack of the disease while others have long, protracted chronic rheumatic activity that leads to cardiac disability.

Since most of the focus of this symposium is on clinical problems, I do not want to belabor any theoretical considerations. I am sure that Dr. Rammelkamp in his presentation tomorrow will cover this ground much more thoroughly. I did want to open on this positive note, because I think this one fact leads to important implications regarding clinical management; namely, the use of prophylaxis in known rheumatic patients and the early treatment of streptococcal infection, both of which measures can be expected to reduce the incidence of rheumatic heart disease.

The next category of problems that one might consider are those concerned with the diagnosis of rheumatic fever. This involves some rather significant and important unsettled questions. Most of you are familiar, I think, with the original statement published

by the late T. Duckett Jones, suggesting certain criteria for the diagnosis of rheumatic fever. This has been recently revised by a committee of the American Heart Association and distributed widely to physicians throughout the country. These criteria can be used to establish a probable diagnosis. There is at the present time no single laboratory or clinical test that, in and of itself, positively establishes the diagnosis of active rheumatic fever. It is true that there are combinations of observations, such as the existence of certain types of heart disease and particular laboratory and clinical findings that make the existence of active rheumatic fever extremely likely.

Periodically there is introduced into the literature of rheumatic fever a new test for the disease. It is not impossible that at some future time one of the new tests will truly be specific for rheumatic fever, but such has not been the case up to the present. It seems characteristic in this field, and I think probably in others as well, that each new test is accepted as the most likely one to be correct, particularly if it is relatively simple and the reagents are commercially available.

This has been true, I think, of the C-reactive protein test. This test is valuable for the establishment of some abnormality common to many diseases, but it is not a specific test for rheumatic fever as is sometimes erroneously believed.

The problem of devising a specific test is not inconsiderable in that such a test can only be validated by appropriate correlation with clinical or pathologic studies.

It should be emphasized, however, that careful analysis of clinical and laboratory findings and proper use of the type of reasoning that has been employed in the Jones' criteria, leads to proper diagnosis in the vast majority of patients.

I turn then to the last part of this presentation to speak about the problem of therapy. This was already mentioned in the previous symposium and I think that it is necessary to clarify some of what has been said.

I am afraid that I must differ with the viewpoint presented by Dr. Gasul. I cannot accept that it is established that the adrenal hormones are an effective therapy of rheumatic fever. I think that this statement needs considerable qualification. First, a brief comment about his statements regarding the Cooperative Study. I would like to correct the statement that both acute and chronically active patients were pooled in this analysis. This is not so. It is true that patients who had been sick for some time were included in the study, but the results obtained were analyzed separately. The type of patients studied were strictly defined, both with respect to the duration of illness and the criteria for admission to the study.

As for the problem of dosage and length of administration of the drug; it is true that at the present time many investigators are using very much larger dosages of drugs than were then used and *then* thought appropriate. It is also true, however, that some of the studies, which have shown the most striking results, did not use any larger dosages than were used in the Cooperative Study, but they do differ in that these were not controlled studies. The types of cases used were not properly defined.

I think that Dr. Ernstene, in his presentation, emphasized an important point that is pertinent to the question of hormones in rheumatic fever and possibly to many of the other questions that this panel will discuss. The very fact that a question cannot be settled by a large number of investigators studying many patients for a long time suggests that the agent is probably not completely effective. When a therapy appears that is really effective, reasonable investigators can quickly agree on the results. It was unnecessary to carry out a cooperative study to demonstrate the effect of penicillin on infections. It was clear to everybody, and only a few patients needed to be studied.

My own opinion regarding the present situation with respect to the use of hormonal agents in the treatment of rheumatic fever is as follows: I think all the studies have shown that certain of the manifestations of acute rheumatic fever are dramatically controlled by hormones. I am referring to such things

as fever and polyarthritis. There is no question that the sedimentation rate returns to normal much more rapidly than it does with salicylate therapy, although it is probably true that salicylates specifically affect acute rheumatic fever. These questions, however, are not critically important to most of us concerned with the treatment of acute rheumatic fever, because the control of these manifestations has never been a major problem and can be accomplished with salicylates. Except for the patient who is severely ill with pancarditis or rheumatic pneumonia, the control of fever is not a great problem.

The question with which we are all concerned is whether this therapy prevents the rheumatic process from producing myocardial and endocardial damage of the type that leads to structural heart disease. This is really the question to which we are all trying to find the answer. At the present time I believe there are no studies that finally settle this problem. Under the conditions used in the Cooperative Study there was no evidence that there was a real difference between the 2 groups of patients.

I think that it is a mistake to underrate the statistical approach and contend that it means nothing about the individual patient. It means a great deal because the statistical approach is a summation of what has happened to that large group of individual patients. When we indicate that something is statistically significant, we mean that there is a high probability that the treatment is effective. This is exactly the information we must use in the treatment of patients. We are always weighing probabilities as to whether or not the treatment employed is effective. Statistical studies give us direction.

It is possible that with larger doses or newer agents given for longer periods of time the results of hormone treatment are different. We are conducting a controlled study at the present time to arrive at an answer to this question.

I suspect, if I have to make a conclusion at present, I would guess that the greatest impact of hormone therapy has been to make investigators conscious of handling rheumatic fever carefully and to control streptococcal infections. This has probably had as much to do with preventing rheumatic heart disease as the hormones. But again, this remains an unsettled question in cardiology and pediatrics.

I think it is not the purpose of this symposium to try to conclude by giving a recommendation, you must take it with a grain of salt.

MODERATOR KATZ: Now we turn to Dr. Hecht who deals with cor pulmonale, arrhythmias, and with valvular regurgitation.

DR. HANS H. HECHT: The large package of unsettled questions that Dr. Katz just handed me contains some problems to which we not only have no answer, but perhaps have been unable to phrase the question. A medical scientist can run into more unsettled questions during a day's work than he could hope to answer in 10 years. From the parcel assigned to me, I shall pick a few problems which should illustrate that many seemingly simple questions have remained unanswered in spite of the apparent advances of recent years.

Cor pulmonale, as an example, is usually considered an unpopular subject because it is a clinically and physiologically poorly defined condition with a wide spectrum of clinical manifestations. One can clearly separate 2 major forms of cor pulmonale. This classification, at least to me, has been helpful in sorting out a number of unrelated conditions. On the one hand, there is the patient who develops a reasonably pure picture of right heart failure, secondary to an overload placed on the right ventricle. These are the cases of heart failure secondary to severe pulmonary vascular obstruction on the basis of "idiopathic" pulmonary hypertension (pulmonary arteriolosclerosis), or pulmonary hypertension secondary to multiple repeated small embolic episodes, or to large emboli occluding major segments of the lung, to valvular or postvalvular stenosis of the pulmonary artery, and to the pulmonary vascular changes secondary to mitral stenosis. These subjects show clear, predominant, right ventricular

hypertrophy by whatever means you choose to detect this together with a low cardiac output. They have little if any arterial oxygen unsaturation, no impairment of respiratory function, and no polycythemia (except under special circumstances). These are the patients who have the highest persistent pulmonary arteriolar resistance measured in human subjects. Though there are many unsettled questions with respect to this syndrome, as for instance the mechanisms by which pulmonary arteriolar sclerosis comes about, I shall not further dwell on this group of patients.

The other type of cor pulmonale is best described as "emphysema heart disease," and is associated with severe ventilatory impairment. These patients show arterial desaturation and polycythemia. The pulmonary artery pressures in these subjects are usually also elevated, but at least at rest not to the extent seen in the first group, their cardiac output is normal, and pulmonary arteriolar resistance is only moderately elevated. Since we know that anoxia alone, and polycythemia alone do not cause heart failure or pulmonary vascular changes of any magnitude, the main question in this group of patients arises, "Why does heart failure occur?" If one examines these patients carefully, however, one finds certain unmistakable derangements that we have come to associate with heart failure. This is particularly true of renal function which shows clearance values and high filtration fractions so characteristic of congestive heart failure. The kidney then cannot tell whether output is high or low but is sensing an abnormal situation. It appears that rather than output alone or tissue tension alone, the amount of oxygen delivered per unit of time, the oxygen transport, expressed as the product of oxygen content times flow, may be one of the determinants of congestive failure. This value would be expected to be below normal if either flow is low or oxygen content is low. The latter situation can be compensated by better than normal flow values. The maintenance of a normal oxygen transport in the face of arterial desaturation would, therefore, require an increased cardiac output. This is the case in otherwise normal subjects and in patients with emphysema without evidence of cardiac disease. One must assume that in cor pulmonale of the emphysema heart variety, the cardiac output is not so high as it should have been to overcome the deficiency in transport, and that similar to the situation in so-called "high output" heart failure, the heart is not working as hard as it should under the given circumstances. One must therefore implicate a myocardial factor as an important cause of heart failure in severe emphysema. We do not know whether this is true, and what this factor might be. It is interesting to note, however, that heart failure in emphysematous patients usually occurs in the older age group. Emphysema heart might be a form of degenerative cardiac disease, whose manifestations are brought about and colored by the simultaneous presence of the pulmonary ventilatory changes and the resultant anoxia.

Another important problem often discussed in the management of these patients has to do with the treatment of the polycythemic states. Is blood letting indicated under all circumstances? To understand this, one must keep in mind that a severely polycythemic state, let us say with volumes of packed red cells between 70 and 80 per cent, gives rise to a series of symptoms that are not necessarily the direct consequence of pulmonary dysfunction. These symptoms are similar to those encountered in patients with polycythemia vera, and presumably have to do with the marked increase in the total circulating blood volume. These can be improved by blood letting. It is the relief of plethora that these patients acknowledge. The symptoms that are due to the underlying primary disease of lung and heart are not ameliorated, nor can one demonstrate any improvement in either pulmonary or cardiac function, vascular pressures, arterial oxygen saturation, or carbon dioxide tension following frequent phlebotomies. Inasmuch as one might consider polycythemia as the only attempt available to the organism to return oxygen transport values to near normal, bleeding such patients might

even interfere with this admittedly feeble response and one can precipitate heart failure by frequent phlebotomies in such patients. On the other hand, changes in the apparent viscosity of the blood at levels above 70 per cent of packed red cells will make bleeding necessary, and on this basis phlebotomies are indicated. If this sounds complicated, it is, and the practical conclusion is to stay on the middle road: bleeding a subject with a volume of packed red cells above 70 to values in the low 60's might improve or ameliorate the symptoms of plethora and overcome the deleterious effects of changed viscosity at high hematocrit levels, and at the same time leave the patient with a somewhat increased red cell mass available for oxygen transport.

The field of cardiac irregularities must seem to many of you to present little, if any, problems except from a purely diagnostic standpoint. Indeed if one goes over the masterful analyses in the books by Wenckebach, Sir Thomas Lewis, and lately by Katz and his associates, one wonders why this topic should indeed be included in a panel on unsettled questions. But here again, more studies have raised more questions. I need not mention the perennial controversy concerning the nature of fibrillation and flutter. To me this is still an unsettled question, though it seems to be settled in the minds of some investigators. The trouble is that these apparent settlements differ from one group to another and none of the proposed solutions is universally accepted. From some observations based on micro-electrode recording of single cardiac cells, it is possible that neither of the 2 most popular concepts, the circus rhythm theory and the single focus theory, may have the final answer.

Another question that is frequently asked deals with the problem whether conversion of atrial fibrillation to a normal sinus rhythm is always desirable, not only on the basis of prevention of embolic phenomena, but also for reasons of improving cardiac function by restoring a coordinated atrial contraction. No one denies that conversion to sinus rhythm will reduce the dangers of right and left-sided emboli, particularly in subjects with rheumatic valvular disease. The argument is of lesser value in patients with atrial fibrillation associated with high flow values, and seems of lesser concern in patients with arteriosclerotic heart disease and normal-sized hearts. The ventricular function of atrial fibrillation as compared to that observed in normal sinus rhythm has been examined frequently, and it is usually stated that the onset of fibrillation is associated with a sharp fall in stroke volume and cardiac output. This is true in the acute experiment where the onset of atrial fibrillation is generally accompanied by a high ventricular rate. If the ventricular rate is brought under control at rest as well as on exercise, one cannot demonstrate a significant influence of the atrial contraction upon cardiac filling and cardiac output, at least not by the relatively crude measurements available to us today. It is true, however, that even on mild exercise, patients with atrial fibrillation usually show an unbridled tachycardia and it may be that this particular factor is responsible if heart failure occurs as the result of atrial fibrillation alone. Using flow values and simultaneous left heart pressure tracings one can very precisely quantitate the influence of the left atrium on cardiac filling from instant to instant, and these studies seem to have shown that atrial systole is mechanically fairly ineffective.

In the extrasystolic types of irregularities, which include paroxysmal atrial, and ventricular tachycardia, the question might be raised how the advances in modern surgical technics might influence our course of therapy. There are cases in which it is difficult, if not impossible, to arrest the disorder. Examples may be cited where gangrene of the extremities, heart failure, and even death occurred as the consequence of the uncontrollably high ventricular rate. Modern surgery has advanced to such a degree that it seems entirely feasible to consider surgical interruption of the atrioventricular pathways in nodal or atrial tachycardia in desperate cases, and artificial cardiac arrest by means of a bypass circulation in ventricular paroxysms. These are spec-

lative thoughts, but there is no reason why these newer advances could not be used to advantage as a last resource.

In cases of complete atrioventricular block and Adam-Stokes seizures, the use of external pacemakers has been advocated. I have no experience in this field, but I gather that the ultimate salvage is not high. One should remember, however, that these efforts are really still at their beginnings and there is no reason why an automatic pacemaker could not be placed on or within the chest to be active for long time periods.

Akin to these problems are those concerned with patients who develop sudden ventricular fibrillation. The surgeons have shown that such episodes occurring as a result of cardiac manipulation or otherwise during surgery are not too difficult to deal with. We are now accustomed to hear talk of "good" and "bad" ventricular fibrillation, presumably the surgeons' definition of ventricular flutter versus ventricular fibrillation. The differentiation is used to predict the response to defibrillation. An extremely difficult question deals with the nonsurgical patient who suddenly develops ventricular fibrillation perhaps in the wake of a coronary occlusion or as a sign of myocarditis. Is one to open the chest in the office, on the wards, or wherever he is, massage, and defibrillate the heart? I doubt that a definite answer can ever be given. At the moment, I believe that in young subjects in whom we suspect myocarditis, such a procedure is warranted and we have done it in such cases. In patients with acute myocardial infarction, the question is more delicate and depends somewhat on the size of the infarct. If the infarct appears small and the patient is relatively young, I believe such drastic procedures may be indicated as they might be in those in whom the infarct is ushered in by an attack of ventricular fibrillation. Since no more than 3 minutes must elapse between the onset of fibrillation and cardiac massage, time is exceedingly short and therefore this problem becomes acute only in very few instances. There will be irreparable brain damage if a longer time interval has elapsed, and no attempt should be made to open the chest if more than 5 minutes have elapsed. For those who will have an opportunity to battle with death directly in this manner, I should like to remind you to open the chest widely, have an assistant spread the ribs, and split the pericardium before massaging the heart. Defibrillation through the unopened thorax is possible but not as yet safe and reliable.

Finally a remark concerning still another field in which many unsettled questions remain, though a great many have been answered during the last few years. This has to do with the precise quantitation of valvular disease. This may decrease in importance as soon as open heart surgery replaces the present technics. In cases of valvular stenosis, the use of flow determination coupled with pressure measurements across the involved valve has made a quantitative assessment of the stenosing process possible. The estimation of regurgitation, however, has been difficult, and is still by and large an unsatisfactory problem, since one cannot rely on the physical signs of valvular regurgitation to be of help for a quantitative diagnosis. The use of indicator-dilution curves, a method of tagging blood with readily identifiable substances will provide the desired answer. By this means, one should be able to quantitate the volume of shunted blood through a given valve area. None of the present methods is satisfactory but I am quite confident that the solution is close at hand. Once such an approach can give us reasonably precise values for regurgitation, we can improve our clinical diagnosis of such lesions and provide much needed preoperative information to the surgeon. We shall then also be able to answer still another unsettled problem, namely the role that altered myocardial function plays in the symptomatology of valvular heart disease.

MODERATOR KATZ: We will next turn to Dr. Burch, who will undertake to discuss heart failure and anxiety states.

DR. GEORGE E. BURCH: There are many unsettled problems in this field. Any physician who has treated a patient with congestive heart failure who died in spite of every form

of therapy becomes aware of many unsettled questions not only in management but also in interpretation of clinical manifestations.

One problem still unsettled is the diagnosis of congestive heart failure. Too often it is taken for granted that the diagnosis can be made readily and with certainty, but in older people there arises the problem of differentiating congestive heart failure from emphysema or chronic pulmonary disease or of differentiating the role of chronic pulmonary disease from that of heart failure when the two co-exist.

We do not devote sufficient time to the solution of our problems, including a study of the patient at the bedside. We are so hurried and so overburdened with patients or other problems that we do not devote as much time to our patients as we should. For accurate diagnosis and satisfactory management of patients, more time is needed to obtain meticulous histories in an effort to evaluate the cardiac state and to make accurate decisions. I think that one of the greatest shortages of the physician today is time. This needs attention to improve the practice of medicine.

As for the diagnosis of congestive heart failure, the best we can do, of course, is to use adequately the methods available. Eventually, methods must be developed to measure the efficiency of the heart so as to define quantitatively its work, cardiac reserve, and changes in reserve as therapy and management progress. The ballistocardiogram was introduced to solve that problem, but its value remains controversial. Whether or not pressure-volume loops and derived time-course curves of work and power can be obtained simply and satisfactorily in the near future is also still unsettled. Such information may also settle the problem of transposing observations on animals to man. Whereas experiments on dogs and rats are relatively simple to perform, sweeping conclusions cannot be made that they apply to diseased human beings as well. Many errors today have resulted from such conclusions, further erroneously fortified by biased selection of confirmatory data with absolute disregard for contradictory observations. Accurate quantitative data regarding cardiac work would eliminate greatly such practices.

More information is needed about the physical chemistry of muscle contraction. Muscles have been contracting for many thousands of years, but we still do not know the time-course of the physical-chemical phenomena involved in disease of muscle, or the time-course of action of drugs upon these physical-chemical events. These are certainly important problems that need to be solved and would assist in understanding the time-course of variations in membrane potential, the role of ions, the value of potassium, the effects of digitalis, and many other factors which in time would lead to a better understanding of the management of failure of the heart as a pump and, in turn of the great problem of congestive heart failure.

Another problem is the aging process. What does the natural process of getting older do to the heart? How does the passage of time make the heart more vulnerable to stresses that the young heart supports with impunity? Is there such a thing as degeneration of function of the heart or any organ only because of aging, or must there be associated changes other than merely becoming older? These are exciting unsettled problems.

Volume regulation is another unsettled problem. What determines the amount of fluid and electrolytes that should be in our bodies at any moment, the time-course of the precise location of water and electrolytes, the time-course of net shifts, and how shifts occur without producing disturbances in man's health but rather to ensure better health under varying circumstances? There is evidence to support the idea that a volume regulatory mechanism might be located in the right atrium and partly in the pulmonary veins.

The role of the venous system, and of veins in general, in congestive heart failure remains obscure. The more thoroughly veins are studied in congestive heart failure, shock, and some of the reactions to systemic infections, the more it is realized that they constitute an extremely important functional segment of the circulation.

The problem of water and electrolyte bal-

ance in congestive failure must be confronted. Physicians rather arbitrarily and haphazardly prescribe for patients diets and drugs that strongly influence water and electrolyte balance. If Harvey's prescriptions were reviewed, they might be ridiculed, although he practiced superior medicine for those days. Few of those practices would be used today, just as few of our present prescriptions would be used 50 years hence. In fact, many physicians today can ridicule their own prescriptions of the past for the treatment of pneumonia. We need to know more about the many things we do empirically daily in the practice of cardiology. Until we can measure the state of intracellular water and electrolytes, we shall continue to guess about the management of patients with water and electrolyte disturbances. A simple method is needed to determine the state of the water and electrolytes within cells.

The action of digitalis and of diuretic agents remains as another unsolved problem. The ideal diuretic is yet to be obtained. Certainly, we should use diuretics and digitalis, even though their action is not precisely known, but a great deal remains unknown in these broad fields.

One of the most serious problems that confronts cardiologists today is that of the dilated heart. Considerable time is devoted to work on congenital defects, which the physician encounters once or twice a year, but comparatively little on large hearts, which he sees extremely frequently. When confronted with a patient with a large, flabby, dilated heart, the physician may even remove the cause. He may reduce the blood pressure and correct the aortic stenosis, but the heart may still remain dilated and failure may gradually develop, with resultant death. A method is needed to reduce the size of the dilated heart, possibly by use of a "cardiotonic" substance to shrink the heart and permit it to perform more efficiently. We have been able to show in our own work that a dilated heart is a disadvantage. Despite Starling's law, the advantage of dilatation is limited, and beyond a certain point dilatation makes things progressively worse.

How can the large heart be reduced in size? Digitalis, decreased intake of sodium, and rest certainly help, but the heart still remains large in most instances. Long periods of bed rest, i.e., 6 months or more, are important, particularly if cardiac enlargement is due to myocardial degeneration or to cardiac inflammation.

We still have not found a method of approaching the patient to avoid precipitating cardiac neuroses. With less haste in the management of our patients, statements can be avoided that are apparently innocuous to physicians but are considered ominous by patients. Such statements as "There is nothing wrong with you except a leaky valve." or "Your coronaries are not wide open." are likely to upset anybody. If the patient is properly approached, such provocative statements that may precipitate neuroses can be avoided or satisfactorily explained to prevent an anxiety neurosis. Certain patients that are more prone to develop anxiety states must receive special consideration. Serious thought should be given to ensure relaxation and satisfactory care of the cardiac patient without producing neuroses.

The mechanism by which psychologic disturbances affect the heart is not known. In fact, the relation of the nervous system to health and disease of the cardiovascular system is not only poorly understood but is neglected today in research. There is no doubt that the electrocardiogram can be changed by psychologic disturbances. The chemical state of the fluid of man can be changed by the central nervous system. Renal function is certainly influenced by psychologic and neurogenic factors. The mechanism by which the central nervous system affects the heart and blood vessels, and the methods of interpreting these influences with and without the use of drugs need study. The cardiovascular system, including the important coronary arteries, is influenced significantly by the central nervous system almost constantly and, therefore, should be understood.

In summary, many problems remain to be solved. The pressure of time, which prevents adequate, meticulous care of ill people, must

be combatted. More well-trained doctors and solution of economic aspects of meticulous patient care are needed. We should take inventory to learn whether or not we are accumulating accurate, reliable data upon which to base our judgment in the management of our patients. After all, no conclusion can be any better than the data obtained from examination of the patient.

MODERATOR KATZ: Now we will turn to our last panelist, Dr. Parker, who has undertaken to cover the subject of surgery in congenital, valvular, hypertensive, and peripheral vascular disease.

DR. ROBERT L. PARKER: The rapid advance in cardiovascular surgery has settled a number of questions that were previously unsettled but it has also created many more that are not settled and I should like to propose 7 or 8 questions that now are frequently brought under discussion and concerning which there is variable opinion.

The first question concerns the indications or contraindications for surgical closure of atrial septal defect. This common congenital malformation is one that is often well tolerated by the patient even when a large arteriovenous shunt exists. One then may well question whether the surgical risk of closure is justified when symptoms of cardiac disability are minimal. This defect can now be closed by various surgical technics, either with or without the use of extracorporeal circulation. The risk of surgical closure in the uncomplicated case without increased pulmonary vascular resistance is now approximately 2 per cent. In my opinion, it is now advisable to recommend surgical closure in these patients. Certainly the risk of the subsequent development of pulmonary hypertension or heart failure is much greater than the present risk of surgical closure of the atrial defect. The factor determining high risk in closure of atrial septal defect is increased pulmonary vascular resistance with pulmonary hypertension. Not all patients with atrial septal defect, even when the defect is large in size and the pulmonary flow is excessive, develop pulmonary hypertension and it is still unknown why some do and some do not develop this complication. When there is evidence of mild pulmonary hypertension with the pulmonary artery pressure in the neighborhood of 45 to 60 mm. mercury and pulmonary flow is still high, surgical closure is urgent; in our experience once pulmonary vascular resistance begins to increase it may progress rapidly to a level that would make closure extremely hazardous and in some instances contraindicated. When pulmonary vascular resistance reaches a level of approximately 600 dynes sec.-cm.$^{-5}$ and there is gross arterial desaturation from reverse shunt through the defect, our experience would indicate that surgical closure is contraindicated. Approximately 10 per cent of individuals with suspected atrial septal defect are found to have the atrioventricular commune or "septum primum" defect either in its partial or complete form. The presence of this defect can now be recognized with remarkable accuracy by the characteristic changes in the electrocardiogram in contrast to the usual patterns of right bundle-branch block with normal axis found in atrial septal defect. This constitutes an important point in diagnosis for it is the opinion of my surgical colleagues that the atrioventricular commune lesion should be closed only under direct vision with the aid of extracorporeal circulation.

In ventricular septal defect it is again the question of increased pulmonary vascular resistance and pulmonary flow that constitutes the dividing line separating those cases in which surgical closure can be carried out with low risk from those in which the risk of closure is extremely high, if not prohibitive. Fortunately most young patients with ventricular septal defect not associated with pulmonary stenosis have high pulmonary flows and with only moderate increase in pulmonary vascular resistance and these can be closed with the surgical risk of approximately 5 per cent. The principal postoperative hazard is heart block. In infants and young children with ventricular septal defect who are doing well without evidence of poor exercise capacity, pulmonary edema, or heart failure, su-

gical closure can and should be delayed for the risk of surgery with extracorporeal circulation is much higher in infants and children below the age of 2. In those patients with ventricular septal defect in whom pulmonary flow has become reduced because of the development of high pulmonary vascular resistance and this resistance approaches or exceeds the systemic vascular resistance and there is bidirectional shunt through the defect with arterial desaturation, surgical closure is contraindicated.

A third question in relation to surgical treatment of congenital heart disease that is now frequently asked is the question of the preferred surgical procedure in the treatment of pulmonary stenosis with ventricular septal defect, or Fallot's tetralogy. Is open heart surgery with removal of the stenosis and closure of the ventricular septal defect now the preferable procedure and does it carry a sufficiently low mortality rate to replace the palliative anastomotic operation of the Blalock-Taussig or Potts type? My surgical colleagues have found it necessary to perform an anastomotic procedure only once in the past 2 years and this was in an infant with pulmonary atresia. Although at first our surgical experience with the correction of tetralogy of Fallot by open heart surgery was somewhat discouraging, it is apparent now that the latter procedure can be carried out with as low a risk, if not lower, than that which we found with the original anastomotic procedures. I think I can say without reservation that open heart surgery with extracorporeal circulation is the procedure of choice in the treatment of this malformation.

The fourth question is one that was discussed briefly in this morning's panel and concerns the evaluation of the need for surgical treatment in the patient with mitral stenosis who has suffered one or more systemic embolic complications. I think that the need for commissurotomy in patients with mitral stenosis who have significant disability is no longer an unsettled question. The difficulty that we all face is the accurate diagnosis of associated mitral insufficiency and the determination as to whether it is hemodynamically the dominant lesion. Progress is certainly being made in this field of quantitation of mitral insufficiency, particularly with the newer dye-dilution and special catheterization technics. Approximately 15 per cent of patients with mitral stenosis who present themselves for evaluation for mitral commissurotomy have sustained a previous systemic or cerebral embolism. It has been recognized that the surgical mortality is higher in this group and that the incidence of embolism during surgery is increased. It has also been determined however that the incidence of subsequent systemic embolism has been greatly reduced in those patients with previous history of embolism who have had a successful commissurotomy. It would appear to us that the balance of risks would favor commissurotomy in these patients unless the embolism alone has produced a state of marked incapacity. It is usually preferable for the patient to undergo a short period of anticoagulant therapy preceding surgery.

A question that remains unsettled is how important is re-stenosis following commissurotomy? In view of the basic pathology of mitral stenosis I think we are all amazed how infrequently true re-stenosis seems to occur. Failure of improvement in those cases that have a heavily calcified immobile valve with fused and rigid chordae should not be considered as re-stenosis but rather a surgical failure to relieve the stricture. It is a fact, however, that re-stenosis may occur in a patient who has had a pliable valve at surgery and on whom an excellent commissurotomy has been carried out; this may occur in the absence of a clinical history to indicate recurrent active rheumatic infection. Fortunately, re-stenosis of this type, in our experience, has been rare, involving only approximately 2 per cent of the patients operated.

Another question that is certainly far from being settled involves the criteria for selection for surgery of patients with aortic valvular disease. Aortic insufficiency of moderate degree is in most instances tolerated by the patient remarkably well. The insertion of a

Hufnagel valve is at best a palliative procedure; yet there are a number of patients with pure aortic valvular incompetence who, when symptoms of heart failure develop, need this help. We all hope that a more corrective surgical procedure will be available in the near future.

The surgical treatment of aortic valvular stenosis carries a surgical mortality far greater than that in mitral stenosis and the benefit of surgery is much less predictable regardless of the surgical approach and technic employed. This no doubt is due primarily to the difficulty in approach to the aortic valve as well as the pathologic anatomy itself of severe aortic stenosis. The clinical features of aortic stenosis do not in my opinion allow sufficient accuracy in determining the severity of aortic stenosis to allow surgical attack on the valve without measurement of the pressure gradient across the valve prior to surgery. Although it may well be true that the surgical mortality and the benefit from aortic valvulotomy would be more favorable if cases were operated on before the onset of exertion angina, exertion syncope, and symptoms of left ventricular failure, yet it is the opinion of our group that aortic valvulotomy for aortic stenosis is justified only when symptoms of severe and progressive incapacity exist. I think we are in need of more specific information with regard to the prognosis of aortic stenosis when left ventricular hypertrophy or early signs of decreased effort tolerance became manifest. Certainly the criteria for selection of patients for surgery for either aortic stenosis or aortic insufficiency remains unsettled.

I am asked frequently whether surgical sympathectomy still has a place in the treatment of patients with severe essential hypertension and I think the answer is a qualified, "yes." Sympathectomy has been performed on only a very few hypertensive patients in the past few years at the Mayo Clinic. Occasionally, however, we see a young individual with severe hypertension, with normal renal function, and in whom renal artery obstruction has been excluded, whose hypertension has not been controlled with antihypertensive drugs. Such a patient may benefit from surgical sympathectomy. It is not possible, in my opinion, to predict what benefit may result from a sympathectomy but there is no doubt that occasionally the result is most gratifying.

In this discussion of unsettled questions in surgical treatment of cardiovascular disease I shall not go beyond the aorta, and my final question concerns the difference in need for surgical treatment of abdominal aortic aneurysm as compared to thrombotic aorto-iliac occlusion. The life expectancy of patients with abdominal aortic aneurysm is poor. The 5-year survival in abdominal aortic aneurysm according to the studies of Massarelli and Estes is 18 per cent and death in the majority of cases is due to the aneurysm. Even though the surgical mortality is high, 8 to 10 per cent, for resection of the aneurysm, this is a surgical mortality that is well justified considering the seriousness of the lesion. If the patient with abdominal aortic aneurysm has no other disease that constitutes an equal or greater hazard to his future, one can well recommend it, in fact urge resection of the aneurysm.

In contrast to the mortality from the abdominal aortic aneurysm, the life expectancy of thrombotic occlusion of the terminal aorta is good. The 5-year survival rate is 72 per cent according to the same authors and death is rarely due to the aortic occlusion itself but due to other cardiovascular disease. Proximal propagation of the thrombotic occlusion to a level that has caused obstruction to renal flow has not been demonstrated in any of our cases. Surgical resection and graft for an aortic iliac occlusion even though it carries a much smaller surgical risk than that for aortic aneurysm can be justified in my opinion only on the basis of the severity of the claudication and degree of incapacity due to ischemia and not on the basis of the lesion's threat to the life of the patient.

MODERATOR KATZ: I would now like to give each of the panelists a chance to comment about what the other panelists have said. I will start with Dr. Ernstene. Have you any comments to make?

DR. ERNSTENE: No, thank you Dr. Katz.

None of the statements that have been made has sent my blood pressure up.

MODERATOR KATZ: Dr. Burch, will you comment?

DR. BURCH: I agree with Dr. Ernstene. However, I would like to ask Dr. Katz a question. Dr. Katz, you believe, I know, that ingested fats and cholesterol have something to do with the production of arteriosclerosis. Since the pulmonary artery is bathed with food that has been consumed and absorbed, why doesn't it develop there instead of the aorta?

MODERATOR KATZ: I think that it is still an unsettled question. It may be merely a question of the low pressure within the pulmonary arteries. Hypertension is known to aggravate atherosclerosis.

As to the role of cholesterol and fat I would like to say that, while I am thoroughly convinced that cholesterol and fats are definitely behind the problem of atherosclerosis, the problem is not that simple. Other factors are also involved. The relationship is not one to one. Many questions need to be answered before the data can be applied clinically. We still do not know all the answers. We must be careful as to how we jump from animal experiments to application to human beings.

Dr. Dorfman, have you anything to say?

DR. DORFMAN: I don't believe that I have anything to add, Dr. Katz.

MODERATOR KATZ: Dr. Hecht.

DR. HECHT: The remarks that Dr. Parker made concerning re-stenosis lead me to make a brief observation, and perhaps to offer some advice. It is peculiar that only few efforts have been made to measure precisely the result of surgery on the mitral valve. It is a relatively easy matter to measure the mitral valve gradient prior to surgery at the operating table and to check these findings after the valve has been split. One can thus immediately assess the surgical result. It is not infrequent that some stenosis remains, even though the surgeon might feel that the procedure was satisfactory. Occasionally the surgeon is made to re-enter the valve area, to loosen adhesions of the chordae tendineae, and in general to prepare the valve so that no gradient remains. This is not always possible. One wonders sometimes whether in cases of reported re-stenosis, one is not dealing with instances of inadequate surgical repair. Not unless one has definite evidence that no gradient was left at surgery and that a significant gradient reappeared at a later time, is one justified to talk confidently of re-stenosis.

DR. PARKER: I am not certain if Dr. Hecht intended to leave the impression that phlebotomy in patients with secondary polycythemia is of no value. If he did, I would like to register a different opinion. Although it can seldom be shown that phlebotomy to reduce a hematocrit level from approximately 65 to 55 per cent in patients with pulmonary emphysema and secondary polycythemia produces significant improvement in the pulmonary function measurements or in level of arterial unsaturation, it has been my experience that often by reducing the hematocrit level there is a significant symptomatic improvement, especially from the standpoint of headache and a sense of well being and I am sure this is not entirely a psychologic benefit.

Could I ask a question of Dr. Ernstene? I don't believe it was mentioned. I think it is an unsettled question as to whether or not the use of radioactive iodine to produce hypothyroidism has any place in the treatment of severe or intractable angina. I once heard it said that there are no patients with intractable angina; there are intractable patients with angina. Dr. Ernstene, will you comment on that?

DR. ERNSTENE: I would disagree. There certainly are patients who have intractable angina quite aside from their own personal intractability, and I believe radioactive iodine has a definite place in the management of patients who cannot be controlled by the usual measures of treatment.

It has been well established by observations in a number of medical centers that improvement results from induced hypothyroidism in about 75 per cent of properly selected patients. The underlying coronary artery disease is not alleviated, and it has not been established that life is prolonged. Tense, hyperactive persons are particularly suitable candidates. The

treatment should not be employed in patients who have been getting progressively worse or in those who recently have had myocardial infarction. The best results are obtained in persons whose condition has remained more or less stationary or has progressed only slightly over a period of 6 months or more.

MODERATOR KATZ: Does anybody else have a last word before I close this meeting?

DR. BURCH: I would like to come to the support of Dr. Parker about bleeding the patient with polycythemia in association with cor pulmonale. Several of our patients have obtained dramatic benefit from bleeding, which is too frequently neglected in the management of such patients. We bleed them gradually, depending on the clinical state, until the hematocrit level becomes normal; our results have been impressive almost invariably.

MODERATOR KATZ: You see, we have had the traditional kind of panel, each panelist expressing his own viewpoint—sometimes this was in accord with the views of others and sometimes there were disagreements. I am reminded of what a psychoanalyst said about tranquilizer drugs. This psychoanalyst said, "You know peace of mind is a fine thing but what would happen to the world if everyone was agreeable. After all progress in the world has been made by neurotics, by those who disagree."

I regret that time will not permit consideration of the many questions sent up by the audience. But I think your patience has been tested long enough.

I think you will agree that the purpose of the panel has been fulfilled in that it has stressed what we do not know. It has raised many questions still unsettled. It has shown the practicing physician how careful he must be in applying new knowledge and accepting old dogmas as valid. This is not to say that we must chide ourselves for doing so badly in medicine. Actually we are doing exceedingly well, progress has been rapid, but we must not become smug and believe we know everything.

I wish to thank the panelists for their contributions and for so agreeably accepting the manner of conducting the panel that your moderator suggested. And finally may I thank all of you for listening so quietly and patiently to what we have had to say. I hope you have found this session profitable, illuminating, and thought provoking.

Wade, G., and Ball, J.: Unexplained Pulmonary Hypertension. Quart. J. Med. **26**: 83 (Jan.), 1957.

Ten patients with unexplained pulmonary hypertension are reported. Six presented the characteristic picture of an apparently healthy, young female who developed progressive dyspnea with substernal discomfort and fatigue. Effort syncope was common. Physical signs of pulmonary hypertension and a malar flush were found, but there was little cyanosis. Electrocardiogram, fluoroscopy, and cardiac catheterizations were confirmatory. Primary contraction of terminal muscular pulmonary arteries was usually found. In 2 other patients pulmonary hypertension was due to a generalized lung arteritis. Such patients showed, in addition, digital arterial involvement. In 2 patients, cyanosis and hemoptysis were noted. In these bronchopulmonary anastomoses were found. Therapy was largely ineffective.

KURLAND

BOOK REVIEWS

Klinische Onderzoekingen met de Laag-Frequente Ballistocardiograaph Volgens Burger (Clinical investigations with the aid of the low frequency ballistocardiograph of Burger). *H. Elsbach,* Uitgeverij Excelsior, The Hague, 165 pages, 53 figures.

This monograph (in Dutch, but with a brief summary in English) is a record of an extensive clinical experience with the ultra-low-frequency ballistocardiograph designed by Professor H. C. Burger of Utrecht. The author breaks new ground by interesting himself in clinical studies made not only with the well-known force ballistocardiogram, but also by records of its first and second integrals, that is, records of the velocity and displacement of the body's center of gravity. Extensive statistical tables of normal values testify to the care and exactitude of the study, but there are no calibrations published and so no normal standards for amplitude. Examples of the 3 types of records are illustrated for a wide variety of clinical conditions and many deviations from the normal are pointed out. The reviewer is happy to report that a full English translation is soon to be available.

ISAAC STARR

Physical Basis of Ballistocardiography. *A. Noordergraaf,* University of Utrecht Uitgeverij Excelsior—Oranjeplein 96—The Hague, Netherlands, 1956, 146 pages, 85 figures.

This monograph, written in excellent English by a Dutch biophysicist trained in the laboratory of Professor Burger of Utrecht, is characterized by a physical and mathematical approach to the theoretical problems of the ballistocardiogram and, to a lesser degree, to those of the elasticity of the blood vessels and the plethysmograms of the arm and leg. A major part is concerned with problems of ballistocardiographic instrumentation that are approached mathematically by means of formulas long used by physicists in the solution of vibration problems. It is concluded that the ultra-low-frequency ballistocardiogram, when displacement is recorded, gives a good reproduction of the movement of the body center of gravity with time. When velocity and acceleration are recorded, one obtains records related to the momentum and the forces respectively. These records are believed to be more accurate than those secured by high-frequency instruments, or with low-frequency critically damped instruments. The author also attempts the theoretical prediction of the ballistocardiogram and of the peripheral plethysmograms from anatomic and physiologic data already in the literature, with good agreement between theoretical and experimental results. This is an interesting monograph on the physical approach to ballistocardiographic theory and instrumentation, and it contains a large amount of original material.

ISAAC STARR

La Balistocardiographie, se bases physiques et ses applications clinique. (Ballistocardiography, its physical basis and its clinical applications.) *G. -R. Rager.* Paris (6e) Masson et Cie, 1957, 108 pages, 32 figures.

This monograph (in French) is essentially a review and its contains very little original material. There is an excellent and up-to-date review of the modern instruments and the physical principles underlying them, followed by a critical review of our knowledge of the normal ballistocardiogram and its changes in various clinical conditions. There is an extensive and well-chosen bibliography.

ISAAC STARR

Balistocardiografia Clinica (Clinical Ballistocardiography). *Alvarez-Mena.* La Habana, Cuba, M. V. Fresneda, 1955, 333 pages, 83 figures.

This is an extensive clinical study (in Spanish). All the records published in the text have been obtained with a shin-bar apparatus, the only method the author has had access to in his clinical experience. He is well aware of its limitations and makes no attempt to compare his results with those obtained with other technics. The bibliography attached to each chapter is extensive and some hypothetical interpretations of the ballistocardiogram are presented with lucidity and clearness.

ALDO CORBASCIO

Balistocardiografia Clinica (Clinical Balistocardiography). *L. de Soldati;* Buenos Aires, Araucaria, 1957. 422 pages, 127 figures.

A well-documented, very complete, and highly readable review (in Spanish) of the clinical applications of ballistocardiography.

The experimental background and the physical concepts that are of immediate concern to the physician are presented in an interesting fashion together with a review of the various types of ballistocardiographs, their advantages and respective drawbacks.

The treatment of the literature is extensive and accurate. This is one of the most complete works on ballistocardiography that has appeared. The bibliography contains 379 titles.

ALDO CORBASCIO

Balistocardiografia Clinica (Clinical Ballistocardiography). *D. Sibilia.* Roma, S. E. M., 1953. 105 pages, 25 figures.

The author describes a high-frequency table in which the sensing element is constituted by a piezoelectric capsule connected to an electrocardiographic amplifier. The records published are those commonly obtained on high-frequency beds. A record of transverse movement of the chest is also described. The clinical applications of the high frequency ballistocardiogram are discussed and illustrated in detail. To the book has been appended a bibliographic survey complete up to the time of publication. A well-written and attractive monograph, probably the best published in Italy so far.

ALDO CORBASCIO

BOOKS RECEIVED

CIRCULATION is very glad to acknowledge the receipt of the following books. Insofar as space permits, as many appropriate books as possible will be reviewed.

Electrocardiographie Endo-cavitaire. *H. Latour and P. Puech.* Paris, Masson et Cie., 1957, 306 pages, 132 figures. 3,200 fr.

Peripheral Circulation in Health and Disease. *Walter Redisch, Francisco F. Tangco, and R. L. deC. H. Saunders.* New York, Grune & Stratton, Inc., 1957, 154 pages. $7.75.

Chirurgie à Coeur Ouvert. *C. Dubost and P. Blondeau.* Paris, Masson et Cie., 1957, 320 pages, 115 figures. 3,000 fr.

Atti della Società Italiana de Cardiologia. XVII Congresso, Trieste, 1956. Rome, Italian Society of Cardiology, 1957, 510 pages.

L'Année Cardiologique Internationale. Vol. 6. *Camille Lian* and collaborators. Paris, Expansion Scientifique Française, 1957, 360 pages, 66 figures, 17 tables. 2,000 fr.

Monografie Cardiologiche. N. 7: Influenze di farmaci sul quadro ecgrafico della intossicazione digitalica sperimentale. *Piera Pariscenti.* Milan, Società Cromotipografica, 1957, 108 pages, 38 figures.

Bone Disease in Medical Practice. *I. Snapper.* New York, Grune & Stratton, Inc. 1957, 230 pages, 48 figures. $15.00.

Life, Death and Disease in Sweden. *Erik Askupmark.* Stockholm, Almquist and Wiksell, 1957, 56 pages, 10 figures. Sw. kr. 4:75.

The Physiology of Induced Hypothermia. Proceedings of a Symposium. *Robert D. Dripps,* Editor. Washington, National Academy of Sciences—National Research Council, 1957, 447 pages. $3.50.

Maladies des Veines. Diagnostic et Traitement. *Claude Olivier.* Paris, Masson et Cie., 1957, 600 pages, 342 figures. 7.400 fr.

The Anatomy of Congenital Pulmonary Stenosis. *Russell Brock.* London, Paul B. Hoeber, Inc., 1957, 114 pages, 76 figures. $11.00.

La Rauwolfia. Chimica, Farmacologie ed Applicazioni Cliniche. *Livio Meciani.* Milan, Casa Editrice Ambrosiana, 1957, 582 pages, 43 figures.

J.A.M.A. Clinical Abstracts of Diagnosis and Treatment. Selected by *I. Phillips Frohman.* New York Intercontinental Medical Book Corporation, 1957, 564 pages. $5.50.

Modern Medical Monographs, 14. Systemic Arterial Embolism. Pathogenesis and Prophylaxis. *John Martin Askey.* New York, Grune & Stratton, 1957, 157 pages, 22 figures. $5.75.

La Legatura delle Arterie Mammarie Interne nella Terapia della Insufficienza Coronarica. *Guiseppe Gucci.* Florence, Casa Editrice Macri, 1957, 246 pages, 124 figures. 6,000 l.

Le Volume Sanguin des Poumons chez l'Homme. *Jacques Lammerant.* Brussels, Editions Arscia, 1957, 192 pages, 39 figures, 34 tables.

An Introduction to Blood Group Serology. Theory, Techniques, Practical Applications, Apparatus. *Kathleen E. Boorman and Barbara E. Dodd.* Boston, Little, Brown & Company, 1957, 317 pages, 30 illustrations. $7.00.

Atti della Società Italiana de Cardiologia. XIX Congresso, Palermo, 1957. Rome, Italian Society of Cardiology, 1957, 594 pages.

The Electrocardiogram. Its Interpretation and Clinical Application. Ed. 2. *Louis H. Sigler.* New York, Grune & Stratton, Inc., 1957, 312 pages, 195 figures. $8.75.

L'Atrio Sinistro. Fisiologia, Fisiopatologia, Semeiotrica e Clinica. *Bruno Caini.* Florence, Edizioni Mediche Italiane, 1958, 218 pages.

Heart Disease and Pregnancy. Physiology and Management. *C. Sidney Burwell and James Metcalfe.* Boston, Little, Brown & Company, 1958, 338 pages, 44 figures. $10.00.

The Practice of Infectious Disease. *Louis Weinstein.* New York, Landsberger Medical Books, Inc., 1958, 501 pages.

Pathologie et Chirurgie des Carotides. *Georges Arnulf.* Paris, Masson et Cie., 1958, 554 pages, 144 figures. 6,000 fr.

Methods in Medical Research. Vol. 7. James V. Warren, Editor-in-Chief. Chicago, Year Book Publishers, Inc., 1958, 237 pages. $7.50.

An International Symposium on Aldosterone. *Alex F. Muller and Cecilia M. O'Connor,* Editors. Boston, Little, Brown & Company, 1958, 282 pages, 84 illustrations. $8.00.

Etude Radiologique de la Circulation Veineuse du Membre Supérieur (sujet normal). *Ercole Lavizzari and Valerio Ottolini.* Paris, Masson et Cie., 1958, 122 pages, 38 figures. 2,400 fr.

The Lipoproteins. Methods and Clinical Significance. Symposia on Research Advances Applied to Medical Practice, No. 3. *F. Homburger and P. Bernfeld,* Editors. Basel, S. Karger, 1958, 94 pages. $4.00.

Pathologie Vasculaire des Membres. *Pierre Wertheimer and J. Sautot.* Paris, Masson et Cie., 1958, 406 pages, 59 figures. 4,000 fr.

Bepaling van de Circulatie-tijd met een Fotoelectrische Methode (de haemoreflector). Photoelectric circulation time determination. *Salomon Berreklouw.* Amsterdam, Drukkerij Poortpers, 1958, 119 pages.

Einführung in die ballistische Kardiographie. *Ladislaus Michael Rósa.* Munster, West Germany, Regensberg, 1958, 92 pages.

Practical Cardiology. *Albert Salisbury Hyman.* New York, McGraw-Hill Book Company, Inc., 1958, 307 pages. $7.00.

Rehabilitation of the Cardiovascular Patient. *Paul Dudley White, Howard A. Rusk, Philip R. Lee, Bryan Williams.* New York, McGraw-Hill Book Company, Inc., 1958, 176 pages. $7.00.

Auscultation of the Heart. *Abe Ravin.* Chicago, Year Book Publishers, Inc. 1958, 166 pages. $6.00.

Clinical Enzymology. *Gustav J. Martin.* Boston, Little, Brown & Company, 1958, 241 pages. $6.00.

Biophysical Principles of Electrocardiography. *Robert H. Bayley.* New York, Paul B. Hoeber, Inc., 1958, 237 pages, illustrated. $8.00.

Cardiovascular Diseases. Ed. 3 *David Scherf and Linn J. Boyd.* New York, Grune & Stratton, Inc., 1958, 829 pages, 119 figures. $17.75.

ABSTRACTS

Editor: STANFORD WESSLER, M.D.

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ATHEROSCLEROSIS

Laurie, W., and Woods, J. D.: Atherosclerosis and its Cerebral Complications in the South African Bantu. Lancet 1: 231 (Feb. 1), 1958.

It is widely believed that the more severe complications of atherosclerosis such as cerebral and coronary thrombosis are rare among the Bantu. Three hundred consecutive necropsies in Bantu over the age of 19, excluding cases of syphilis and diabetes, indicate that aortic atherosclerosis was prevalent even in younger age groups and its degree and extent increased steadily with age. In 2,000 consecutive necropsies in Bantu patients cerebral hemorrhage or thrombosis was found in 10 men and 21 women. Up to the age of 55, there was no sex difference. Thereafter, women were more prone to cerebral vascular disease with and without hypertension. These findings are presented as evidence refuting the view that the Bantu enjoy any relative freedom from atherosclerosis or its cerebral complications. The high prevalence in Bantu women is contrary to the findings in people of European descent.

KURLAND

Ruskin, H., Cohn, T. D., Bloomberg, B. M., and Greenblatt, I. J.: Serum Betalipoprotein Studies in the South African Bantu. Am. J. M. Sc. **235:** 138 (Feb.), 1958.

The incidence of coronary atherosclerosis has been found to be remarkably low in native Africans. Since atherosclerosis has been associated with an elevation of serum betalipoprotein, the levels of this lipid were measured in several groups of Bantu and the results correlated with dietary habits and clinical data. The adult male and female Bantu were found to have levels of serum betalipoprotein of the S_f 12-100 class that were significantly lower than those of white New York City individuals. The female Bantu had a higher level of the betalipoprotein than the male. The lower intake of dietary fat to levels of 20 per cent of the caloric needs in the Bantu has been regarded as an important factor in producing the low levels of atherogenic serum lipids. Other conditioning factors may be the high carbohydrate intake, exercise, ethnic considerations, liver disease, and the possible increased content of unsaturated fatty acids in their diets.

SHUMAN

Marmorston, J., Magidson, O., Lewis, J. J., Mehl, J., Moore, F. J., and Bernstein, J.: Effect of Small Doses of Estrogen on Serum Lipids in Female Patients with Myocardial Infarction. New England J. Med. **258:** 583 (March 20), 1958.

The authors report the effects upon the serum lipids of the administration of 10 micrograms daily of ethinyl estradiol to 26 postmenopausal women who had sustained at least 1 myocardial infarction. It was noted that there was a fall in serum cholesterol, a rise in phospholipid, and a fall in cholesterol-phospholipid ratio of the same magnitude as reported by other investigators using very large doses. These lipid changes were progressive during the first 6 or 7 months of estrogen therapy and then remained at constant levels despite continued treatment. The effect of estrogen upon the blood lipids was found to be dependent upon the pretreatment pattern. Little or no effect was found when the lipids initially were normal, and the greater the initial lipid abnormality the greater were the changes found

under treatment. These observations suggest that estrogen may have a homeostatic effect upon the serum lipid levels.

SAGALL

Tobian, L., and Tuna, N.: The Efficacy of Corn Oil in Lowering the Serum Cholesterol of Patients with Coronary Atherosclerosis. Am. J. M. Sc. **235**: 133 (Feb.), 1958.

Corn oil was given to 23 patients with coronary atherosclerosis in amounts of 30 to 45 ml. before each meal with minor dietary restrictions in order to appraise its influence upon serum cholesterol and phospholipid levels. The pretreatment cholesterol level averaged 271 mg. per cent. Seventy per cent of the patients had a 15 per cent decrease in serum cholesterol averaging 208 mg. per cent after a period of corn oil feeding. Another 26 per cent of the patients had smaller decreases in serum cholesterol. Corresponding decrements in the level of phospholipids were noted. The drop in serum cholesterol was maintained during a year of corn oil ingestion. None of these patients experienced any exacerbation of anginal symptoms while taking corn oil.

SHUMAN

Zarafonetis, C. J. D., Miller, G. M., Seifter, J., and Baeder, D.: Effect of Prefeeding on the Acute Response to Lipid Mobilizer Hormone in Man. Am. J. M. Sc. **235**: 410 (April), 1958.

The intravenous administration of lipid mobilizer (LM) produced a hyperlipemic response in each of 7 test subjects in the fasting state. Two forms of LM were employed in the study: a dialysate of plasma of cortisonized horses, and a pure crystalline substance derived from the dialysate. The plasma lipid fractions measured included cholesterol, phospholipid, and total fatty acid. Each of these lipid fractions exhibited a 2- to 3-fold rise promptly after LM administration. Prefeeding of the subjects with glucose or cream blocked the hyperlipemic response. However, after amino-acid feeding a rise in plasma lipids could be evoked by LM. The role of the liver in the metabolism of the triglycerides mobilized by LM may govern the rate at which the lipids enter the systemic circulation. Evidence is cited to support the view that the damaged liver fails to metabolize fats in a normal fashion. The prefeeding of glucose may provide glycogen or other factors for improving fat utilization by the liver thereby preventing peripheral hyperlipemia. The prefeeding of fat may activate a clearing mechanism within the liver for the removal of lipids mobilized by LM. Attention is called to the finding that as little as 1.2 μg. of the crystalline LM was capable of inducing hyperlipemia. Further studies with this substance are in progress.

SHUMAN

Weiner, N., Walker, W. J., and Milch, L. J.: Effect of Beta-Sitosterol on Serum Cholesterol and Lipoprotein Levels of Patients Ingesting a Low-Fat Diet. Am. J. M. Sc. **235**: 405 (April), 1958.

Following a period of administration of a low-fat (50 Gm. daily) diet for a prolonged period 21 male patients with proved atherosclerosis were given alternating courses of beta-sitosterols and placebo lipid suspensions. The weight curves and diets remained constant throughout the period of study. Lipoprotein and cholesterol determinations were made serially during the various phases of the investigation. The effect of the agent upon serum lipoprotein levels parallels the action of the low-fat dietary regimen when given over an 8-week period. There was a considerable variation in the individual response to the drug but, in general, significant reductions were recorded in mean levels of the S_f 0-12 and 12-20 classes of serum lipoproteins. Changes in S_f 20-400 lipoprotein and serum cholesterol were not significant. The changes induced by the drug were to some extent additive to those of the low-fat diet. No toxic effects were observed from an oral dose of 10 Gm. of beta-sitosterol over an 8-week period.

SHUMAN

BLOOD COAGULATION AND THROMBOEMBOLISM

Blumberg, H., Dayton, H. B., and Gordon, S. M.: Bronchodilator Action of the Anticoagulant Warfarin Sodium. Science **127**: 188 (Jan. 24), 1958.

Using the isolated guinea pig tracheal chain technic, a method which correlates well with clinical bronchodilator responses in pharmacologic studies, the administration of warfarin sodium was compared with aminophylline. Under the conditions of the experiment described, warfarin sodium possessed about half the tracheodilator activity of aminophylline. This effect was not influenced by the simultaneous presence of heparin. The authors state that if the dilator effect as seen in this study is reflected in the corresponding bronchodilatation in man, it may be possible that the initial injection of warfarin sodium may produce some immediate bronchodilatation as well as initiating the slower anticoagulant activity. Studies are being extended to determine whether this activity is a general property of the 4-hydroxycoumarin anticoagulants.

WAIFE

Coon, W. W., Mackenzie, J. W., and Hodgson, P. E.: A Critical Evaluation of Anticoagulant Therapy in Peripheral Venous Thrombosis and Pulmonary Embolism. Surg. Gynec. & Obst. **106**: 129 (Feb.), 1958.

In a 10-year period, 511 patients having clinical evidence of deep leg vein thrombosis (359) or pulmonary embolism (152) were treated initially with heparin in combination and then with an antiprothrombin drug alone, usually for a total of 10 to 21 days. The desired prothrombin depression of 10 to 29 per cent (Quick activity) was obtained on a minority of treatment days. Thromboembolic complications during or within 12 weeks after therapy were noted in 71 patients and were not demonstrably related to the degree of prothrombinopenia. Similarly, therapeutic results could not be related to the earliness of beginning treatment nor to its duration. Nonetheless, the conclusion was reached that anticoagulation can reduce significantly both morbidity and mortality from these 2 types of thromboembolism. Complicating hemorrhage was seen in minor form in 81 instances and in major form in 13, but all were controllable.

ROGERS

Weismann, R. E., and Tobin R. W.: Arterial Embolism Occurring during Systemic Heparin Therapy. Arch. Surg. **76**: 219 (Feb.), 1958.

In a 3-year period, the authors encountered 10 patients who developed peripheral arterial embolism while receiving heparin. The clinical picture, gross appearance of the emboli, and the autopsy findings suggest a direct relationship to heparin effect on pre-existing, unsuspected, mural, aortic fibrin-platelet thrombi. All the patients had some clinical evidence of cardiovascular disease. Their ages ranged from 46 to 86 years, with a mean of 64 years. The period of heparin therapy preceding an embolic event ranged from 7 to 15 days. The heparin was administered either intravenously or intramuscularly at 6- to 8-hour intervals with the dose controlled by the clotting time as determined by the Lee-White method. A clotting time of 30 to 40 minutes was considered optimal and the daily dose varied from 150 to 500 mg. In 9 patients the emboli were multiple. All of the patients were treated by embolectomy. Six patients died. Fresh emboli extracted at operation were strikingly similar, pale, soft, salmon-colored clots. Histologically these emboli were comprised mostly of fibrin, platelets, and leukocytes; red cells were rare. These histologic and gross appearances were thought to be consistent with platelet and fibrin precipitation over a prolonged period of time and in a location of rapid blood flow such as the aorta. Three case histories are presented in detail and are representative of the entire group. Although the authors continue to use heparin they are aware of the risk of embolization in susceptible persons and have decreased the dose of heparin that they previously thought was desirable. They no longer believe it wise or desirable to establish clotting times more than 2 or 3 times normal.

BROTHERS

Harrower, H. W., Hurwitz, A., and Yesner, J.: The Treatment of Thromboembolism with Aqueous Heparin. Surg., Gynec. & Obst. **106**: 293 (March), 1958.

The effects of heparin administration in 75 patients having mainly thrombophlebitis and in 15 normal persons are described with emphasis on the technical aspects. The subcutaneous route, employing 0.5 to 1.5 mg. of concentrated heparin per pound of body weight every 6 or 12 hours, was used in 52 patients for an average of 12 days with satisfactory therapeutic results in 44. However, significant bleeding or other complications developed in 15 of the 52. Most of these difficulties occurred during the first week of therapy and despite daily checking of the coagulation time, which was considered to be in a therapeutic range in the majority. Blood viscosity studies, although roughly inversely paralleling the coagulation time, appeared to be of little additional assistance in guiding therapy. In acute or postoperative thromboembolic conditions, the intermittent intravenous method of heparin administration through an indwelling polyethylene catheter was thought to be more effective and safer, thus leaving the subcutaneous technic for use in the more chronic conditions, including ambulatory patients.

ROGERS

McEvoy, R. K., Harder, R. A., and Dale, W. A.: Respiratory and Cardiovascular Phenomena Associated with Pulmonary Embolism. Surg., Gynec. & Obst. **106**: 271 (March), 1958.

Generalized or localized pulmonary embolism to the point of fatality was produced in anesthetized dogs by the injection of a starch suspension or of glass beads 100 microns in diameter. A large volume of either type of embolus evoked a similar response consisting of increasing tachypnea, bradycardia, aortic hypotension, and pulmonary arterial hypertension ending in hypotension with right ventricular failure and death. This response was not significantly altered by previous surgical or pharmacologic autonomic nerve interruption. Furthermore, when the arterial pressure was raised in one lung by selectively embolizing it, the pressure in the other lung, which was being maintained by artificial perfusion, did

change. Thus it was concluded that in this experimental setting no evidence of important reflex phenomena could be found and that these pulmonary emboli produced ill effects by mechanically obstructing the pulmonary vasculature.

ROGERS

CONGENITAL ANOMALIES

Haring, O. M., and Polli, J. F.: Experimental Production of Cardiac Malformations. Arch. Path. **64**: 290 (Sept.), 1957.

A method is presented for the experimental production of cardiac malformations. This consists of timed exposures of pregnant rats to increased carbon dioxide tension, with normal or decreased oxygen tension in the respiratory atmosphere. In this paper the histologic findings in the first 40 serially sectioned hearts of the abnormal offspring are reported. All the hearts obtained from treated animals were found to be abnormal. The following anomalies were observed: generalized marked myocardial thickening, 19 hearts; predominantly right ventricular thickening with narrowing of the pulmonary outflow tract, 9 hearts; left ventricular thickening with narrowing of the aortic outflow tract, 11 hearts; incomplete ventricular septation, 5 hearts; incomplete atrial septation, 13 hearts; and aortic arch anomalies, including persistent patency of the ductus arteriosus, 10 hearts. In some of the hearts a combination of developmental anomalies of the cardiovascular septum was observed. None of the 15 control hearts showed any of the above anomalies.

MAXWELL

Swan, H. J. C., Marshall, H. W., and Wood, E. H.: The Effect of Exercise in the Supine Position on Pulmonary Vascular Dynamics in Patients with Left-to-Right Shunts. J. Clin. Invest. **37**: 202 (Feb.), 1958.

This paper presents detailed hemodynamic observations during leg exercise in the supine position in 30 patients with single congenital anomalies. The subjects were subdivided into one group, in which the pulmonary artery systolic pressure exceeded 16 mm. Hg at rest, and another, in which the pressure was below this value. The first group consisted of 7 patients with atrial septal defects, 6 with ventricular septal defects, and 3 with a patent ductus arteriosus. The second group was composed of 7 subjects with atrial and 2 with ventricular septal defects and 5 with patent ductus arteriosus. It was found that in patients with pulmonary hypertension (the first group) the pulmonary blood flow was found to change only slightly during exercise, regardless of the magnitude of the vascular shunt. The pulmonary artery pressure and the pulmonary resistance were increased. On the other hand, there was no consistent increase in pulmonary resistance during exercise in the group without pulmonary hypertension, although there was a definite increase in pulmonary blood flow. Patients with large left-to-right shunts may adapt to the circulatory needs of exercise without major changes in vascular dynamics. The demands on the heart for an increase in systemic blood flow to meet exercise requirements can be met without a concomitant increase in "stress on those portions of the central circulation already overburdened by the presence of the abnormal shunt."

WAIFE

Loogen, F.: The Pulmonary Hypertension in Congenital Heart Disease with High Pulmonary Output (Persistent Ductus Arteriosus, Ventricular and Atrial Septal Defects). Arch Kreislaufforsch. **28**: 1 (Feb.), 1958.

Of 55 patients with persistent ductus 24 showed increased pulmonary arterial resistance; in these, the systolic pulmonary artery pressure exceeded 30 mm. Hg in 13 and 50 mm. Hg in 9. Histologic study of pulmonary biopsies obtained during operation disclosed intimate correlation between pathologic changes in pulmonary vessels and the mean pulmonary arterial pressure. These changes are attributed to increased pulmonary flow, as all cases with pulmonary hypertension decreased the shunt. The electrocardiogram showed high voltage in V_5-V_6 in 29 per cent, but right ventricular "strain" only in patients with pulmonary hypertension. Forty-four patients with ventricular septal defect also showed a first phase with low pulmonary resistance and large left-to-right shunt, a second phase with equalization of pulmonary and aortic pressures (after the sixth to twelfth month), and a third phase with high pulmonary pressure and shunt reversal (after the second to tenth year). In 61 patients with atrial septal defects the shunt was smaller than in those with interventricular or aortico-pulmonary communications before development of pulmonary hypertension, as the atrial pressure difference was small. The third phase of pulmonary hypertension therefore usually does not appear until after the third decade of life, and is always accompanied by morphologic changes in the pulmonary vessels. These changes in all 3 types of heart disease disappear or show considerable regression after operative treatment, if this is undertaken before development of the third phase.

LEPESCHKIN

Wagner, E., Hermanuz, N., and L'Allemand, H.: Contribution to the Genesis of Pulmonary Hypertension in Persistent Ductus Arteriosus Botalli. Ztschr. Kreislaufforsch. **47**: 50 (Jan.), 1958.

Cardiac catheterization in a 25-year-old man disclosed a pulmonary systolic arterial pressure of 160/80 mm. Hg; the catheter penetrated into the descending aorta. The right-to-left shunt was about 0.5 liter per minute while the phonocardiogram showed only a holosystolic murmur. Blood gas studies showed entry of a pulmonary vein into the persisting left superior vena cava, and this, together with congenital increase in the pulmonary resistance contributed to the pulmonary hypertension. In this patient ligation of the ductus was not indicated.

LEPESCHKIN

Schoenmackers, J.: On Valvular Disease in Congenital Cardiovascular Abnormalities. Ztschr. Kreislaufforsch. **47**: 107 (Feb.), 1958.

All of 162 hearts with congenital cardiovascular abnormalities subjected to this study showed a serous endocarditis of the valves and endocardium, which led to the formation of scar tissue and could have been the cause of valvular or infundibular stenosis and atresia. The progressive course of the disease was due partly to failure of the stenotic part to grow with the rest of the heart, but partly to increase of the stenosis due to active serous endocarditis. Prenatal serous endocarditis leading to valvular stenosis or atresia can alone be responsible for the development of a trilogy or tetralogy of Fallot. Primary isthmic stenosis of the aorta may lead to secondary perforation of the interventricular septum.

LEPESCHKIN

CONGESTIVE HEART FAILURE

Gutner, L. B., Moses, J. B., Dann, S., and Kupperman, H. S.: The Use of Prednisone in Congestive Heart Failure. Am. J. M. Sc. **234**: 281 (Sept.), 1957.

Prednisone was given orally in doses of 5 mg. 4 times daily for 1 week and then 10 mg. 4 times daily to 11 patients with varying degrees of congestive heart failure. The effect of this therapy was favorable in 5 patients who experienced a decrease in dyspnea; a decrease in weight was observed in 5, 1 had an increase in appetite with weight gain and a questionable increase in dyspnea. The administration of prednisone produced a decrease in 17-ketosteroids in 8 patients probably due to suppression of endogenous ACTH secretion. An increase in the urinary excretion of sodium was noted in 7 patients, a decrease in 2, and a variable response in 2. The effect on the excretion of potassium was similar to that of sodium. The mechanism of action of prednisone in congestive heart failure may be that of counteraction of aldosterone production by the adrenal cortex. Secondary aldosteronism may occur in heart failure because of impaired hormone metabolism in the congested liver or because of increased hormonal secretion stimulated by low-sodium diets, rising serum potassium or relative dehydration. It is suggested that prednisone may aid in the correction of these defects and thereby ameliorate the cardiac status.

SHUMAN

Bayliss, R. I. S., Marrack, D., Pirkis, J., Rees, J. R., and Zilva, J. F.: Chlorothiazide: An Oral Diuretic. Lancet **1**: 120 (Jan. 18), 1958.

The response to chlorothiazide was studied in 24 edematous patients, of whom 17 had congestive failure. Thirteen had failed to improve on standard therapy including mersalyl. A daily dose of 2 Gm. produced good results in 14 patients. In patients who responded, chlorothiazide caused an approximately equimolar loss of chloride and sodium, usually maximum on the first day. As edema subsided sodium and water diuresis diminished. On the existing intake of sodium chloride, no changes in serum sodium, chloride, or bicarbonate levels were observed, but the serum-potassium level tended to fall, and there was increased loss of urinary potassium. Since potassium depletion may result, chlorothiazide should be supplemented with potassium chloride. A response to chlorothiazide may be evident in patients refractory to mersalyl or, when given with mersalyl, the diuresis may be greater than when either is given alone.

KURLAND

Zöllner, N. and König, E.: Influence of Cardiac Glycosides on the Venous Pressure after Exercise. Ztschr. Kreislaufforsch. **47**: 31 (Jan.), 1958.

In 16 patients with right ventricular failure the increase of venous pressure 30 seconds after exercise in the recumbent position, compared to the value at rest, was greater than in normal persons. After oral digitalization this increase was definitely smaller; the effect of a single injection of strophanthin was not as pronounced. The decrease of the increment of venous pressure can be used to assess the efficacy of digitalis treatment.

LEPESCHKIN

CORONARY ARTERY DISEASE

Weiss, M. M., and Weiss, M. M., Jr.: The Effect of Myocardial Infarction on the Size of the Heart. Am. J. M. Sc. **234**: 129 (Aug.), 1957.

A study was made of 489 patients who survived an acute myocardial infarction for at least 2 months to determine the incidence of cardiac enlargement during the postinfarction period. Only those patients were included who had normal-sized hearts and in whom the onset of infarction could be determined with certainty. Serial fluoroscopic examinations or teleroentgenograms were used to determine heart size. The observations extend over a period of 1 to 10 years. The incidence of cardiac enlargement due solely to myocardial infarction was 2 per cent of the group. Congestive heart failure was present in each of those exhibiting enlargement of the heart. Other factors causing cardiac hypertrophy, such as hypertension, valvular heart disease or cor pulmonale, were not present. The anatomic factors involved in cardiac enlargement were not determined except in 1 necropsied case in which left ventricular hypertrophy was found. Multiple infarctions did not cause cardiac hypertrophy in the absence of congestive failure. The opinion is expressed that myocardial fibrosis or aneurysm may develop over a period of time, leading to congestive failure, which by unexplained mechanisms leads to cardiac hypertrophy.

SHUMAN

Cohen, D. B., Doctor, L., and Pick, A.: The Significance of Atrioventricular Block Complicating Acute Myocardial Infarction. Am. Heart J. **55**: 215 (Feb.), 1958.

An analysis of 68 cases of acute myocardial infarction complicated by high degrees of atrioventricular heart block is presented. This phenomenon was found more frequently with acute posterior than with acute anterior wall myocardial infarction. The immediate mortality rate of infarction in this series was found to be higher than that of myocardial infarction in general. The mortality rate was higher when the atrioventricular block complicated infarction of the anterior wall, or was due to necrosis of the ventricular septum, and increased with the severity of the block. The immediate prognosis of myocardial infarction complicated by atrioventricular block was further aggravated by the factors known to be of importance in determining the immediate mortality rate of infarction in general. The long-term prognosis, however, is those patients surviving the initial episode was not found to be affected by persistence of atrioventricular block.

SAGALL

Myhrman, G.: The Effect of ACTH and Cortisone on Inflammatory Reactions in Myocardial Infarction. Acta med. scandinav. **159**: 239 (Nov. 29), 1957.

Twenty-five male patients with myocardial infarction were treated with ACTH or cortisone to study the effect of these agents on the general course of the inflammatory reaction associated with the infarct. Frequent determinations were made of the temperature, leukocyte count, fasting blood sugar, sedimentation rate, erythrocyte count, and serum iron. The results were compared with those obtained in a like manner from a control group of 25 males with myocardial infarction who were not given steroids. In the patients treated with ACTH or cortisone, the average leukocyte count was higher than in the control group. Aside from this, none of the reactions studied was significantly influenced by the administration of the hormones.

BROTHERS

Cesarman, T.: Serendipity and Angina Pectoris. Preliminary Information on a Therapeutic Finding. Arch. inst. cardiol. **27**: 563 (Sept.-Oct.), 1957.

The action of Iproniazid has been studied in 41 patients with severe intractable angina pectoris. The drug has been given in doses of 150 mg. per day, divided in 3 equal doses. Any other medication used for the treatment of angina was interrupted. No hypotensive agent was used. In all patients the clinical manifestations of angina completely disappeared within 4 to 12 days. If the administration of Iproniazid was interrupted, or if the dose was decreased the symptoms reappeared within 3 to 8 days. During the Iproniazid treatment the electrocardiogram showed changes toward normal. In 26 cases the electrocardiographic exercise test became normal. Collateral and toxic effects noted were: mouth dryness, meteorism, constipation, dysuria, euphoria, somnolence, vertigo, and tremors. These effects were usually not severe; they might however become limiting factors in the use of the drug. The author believes it is unlikely that Iproniazid acts as a vasodilator or as an analgesic. The opinion is advanced that the drug counteracts other substances increasing the oxygen consumption of the myocardium; it is also possible that Iproniazid increases the efficiency of the cardiac muscle. It is concluded that Iproniazid is a new specific agent for the treatment of angina pectoris. It is hoped that the study of its mechanism of action will lead to a better understanding of the pathogenesis of this syndrome.

CALABRESI

Nesterov, V. S.: Clinical and Experimental Aspects of Cardiac Aneurysm. Klinich. Med. **36/1**: 49, 1958.

Of 70 patients with ventricular aneurysm, 67 had myocardial infarction, and 30 of these continued physical work on the first day of infarction while 3 continued it throughout. Of 7 dogs submitted to exercise in the treadmill 2 days after ligation of the descending branch of the left coronary artery, ventricular aneurysm developed in 5.

LEPESCHKIN

Lepeschkin, E., and Surawicz, B.: Characteristics of True-Positive and False-Positive Results of Electrocardiographic Master Two-Step Exercise Tests. New England J. Med. **258**: 511 (March 13), 1958.

Electrocardiographic Master 2-step exercise tests were performed on 243 volunteer students with no evidence of coronary artery disease and compared with those found in 30 patients with a clinical diagnosis of coronary artery disease. False-positive exercise tests were found in 26 per cent of the normal group with the criteria recommended by Master. This figure was reduced to 16 per cent when Master's criteria were modified to permit recognition of false ST-segment depression caused by superimposition of the T_p and U waves in the ST-segment junction. With these new criteria all the true-positive tests of the coronary disease group still remained positive. Comparison of the 37 persons still showing false-positive tests even with the new criteria with the 30 true-positive group revealed that false-positive tests occurred most commonly in women over 40 years old and in individuals with past or present hypertension. Further study of these 2 groups indicated that the combination of criteria for a positive test with the least amount of overlapping, being present in 94 per cent of the true and in only 23 per cent of the false tests was as follows: inversion of the T wave in lead I or depression of the ST-segment junction beyond the continuation of a P-R interval of 0.75 mm. or more, the return of the S-T segment to the base line at this time taking place in the second half of the Q-T interval, and ST-segment depression of 0.5 mm. or more lasting for 2 minutes or more.

SAGALL

Faivre, Gilgenkrantz, Lagarde, Vincent and Frenkiel.: Controlled Hypoxia Test in the Diagnosis of Angina Pectoris. Arch. mal. coeur **51**: 68 (Jan.), 1958.

One hundred and sixty-four patients with typical clinical signs of angina pectoris but with normal electrocardiograms at rest were subjected to inhalation of 9 per cent oxygen in nitrogen for 10 minutes. Thirty five per cent of these had a positive response according to Lev; the electrocardiographic changes had a "subepicardial localization" in 5.5 per cent and were accompanied by pain in 3.7 per cent. Simultaneous registration of peripheral blood oxygen saturation showed that S-T depression appeared at saturations from 60 per cent to 80 per cent. After resumption of air breathing the saturation becomes nearly normal within 1-2 minutes; because of this rapid normalization, the test is considered safer than the exercise test. The hypoxia test can also be given to patients who cannot or will not execute the proper amount of exercise. Thirty patients were submitted to the Master 2-step exercise test some time after the hypoxia test, and 43 per cent showed a positive response, accompanied by pain in 30 per cent. Only 1 patient showed a negative response both to the hypoxia and the exercise test.

LEPESCHKIN

Gerbaux, A., Piéron, R., and Lenègre, J.: Anatomic and Clinical Study of Atrial Myocardial Infarction. Arch. mal. coeur **50**: 983 (Nov.), 1957.

Microscopically identifiable atrial infarction was found in 8 of 768 autopsies of cardiac patients; among whom 198 also had ventricular myocardial infarction. In 5 patients infarction involved the right atrium; in 3, the left. Among 136 published cases the right atrium was involved in 83 per cent, the left in 13 per cent, and both in 4 per cent. The atrial appendage was involved predominantly in 59 per cent. In 4 patients biventricular posteroseptal, in 1 patient biventricular apical, and in 2 patients left ventricular posterior infarction was present in addition to atrial infarction. In 1 patient with mitral disease, atrial infarction was the only finding. Electrocardiographic signs suggestive of atrial infarction were atrioventricular block, atrial ectopic rhythms, inversion of the P wave in leads II and III, and notching of the P wave. Displacement of the P-R segment was diagnostic only if it occurred in the same direction as the P wave, but this finding was very rare.

LEPESCHKIN

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Braunwald, E., and Morrow, A. G.: Sequence of Ventricular Contraction in Human Bundle

Branch Block. A Study Based on Simultaneous Catheterization of Both Ventricles. Am. J. Med. **23**: 205 (Aug.), 1957.

The validity of the classic concept of bundle-branch block was re-examined critically by simultaneous catheterization of both ventricles permitting determination of the temporal relation between the onset of contraction of the ventricles in 7 patients with normal intraventricular conduction, in 5 with electrocardiographic patterns of left bundle-branch block, and in 10 with right bundle-branch block. None of the patients with the electrocardiographic configuration of left bundle-branch block had a significant delay in the onset of left ventricular contraction. Six of 10 patients with right bundle-branch block showed no abnormal delay in the onset of right ventricular contraction. The absence of abnormal ventricular contraction in patients with complete bundle-branch block is not compatible with the concept of a complete interruption of conduction in a main bundle branch.

KURLAND

Giraud, G., Latour, H., and Puech, P.: The Treatment of Nodal Tachycardias by Procaine Amide. An Intracavitary Electrocardiographic Study. Acta Cardiol. **12**: 615 (Fasc. 6), 1957.

Four cases with paroxysmal atrioventricular nodal tachycardia were studied by intracardiac leads during the attack and following intravenous injection of 250 to 1000 mg. of procaine amide. The morphology of the atrial deflection and its temporal relation to the ventricular complexes permitted a precise location of the impulse origin in the upper, middle, or lower parts of the atrioventricular node. Procaine amide suppressed the ectopic rhythm in all 4 instances. One effect was a depression of the rhythmicity of the ectopic focus manifested by gradual slowing of its discharge. In 1 case this was initiated by transient alternation of the cycle length and in another by shifting of the pacemaker within the atrioventricular node. A second effect was prolongation of intraatrial conduction manifested by a delay of atrial depolarization and widening of the atrial complex. Finally procaine amide produced depression of forward and retrograde atrioventricular conduction manifested, respectively, by prolongation of the R-P intervals and dropped ventricular complexes. Disorders of intraventricular conduction occurred in 2 cases before treatment as a consequence of the tachycardia and were induced in 1 by the medication. In all, the ventricular complexes became normal with slowing of the ventricular rate.

PICK

Panchenko, S. M., Subora, L. V., Kurakova, E. I., and Titova, V. V.: Electrode Pastes in Electrocardiography. Klinich. Med. **36/1**: 144, 1958.

The lowest values of contact potentials and polarization potentials are obtained with silver electrodes and a paste containing 27 per cent sodium soap, 7 per cent ammonium chloride, and 7 per cent glycerin, or with tin electrodes and a paste containing 7 per cent starch, 7 per cent glycerin, and 7 per cent stannic chloride. Both pastes contain also 36 per cent pumice and a bacteriostatic substance. Use of gold, nickel, or stainless steel electrodes leads to higher contact or polarization potentials.

LEPESCHKIN

Dussaillant, G., Alessandri, H., and Gomez, G.: The Normal Kinetics of the Right Atrium and Great Veins.. Hyperkinetic Pattern in Tricuspid Stenosis and Other Conditions Hindering Atrial Emptying. (An Electrokymographic Study.) Acta Cardiologica **12**: 569 (Fasc. 6), 1957.

The authors report electrokymographic studies performed in 62 normal individuals and 230 patients with various types of heart disease, with special attention to dynamics of the right atrium and the great veins. The method of choice for an analysis of systemic venous pulsations is an electrokymogram of the right diaphragm which, in contrast to the electrokymogram of the superior and inferior venae cavae, is easy to perform and provides dependable tracings with constant features under normal conditions. In 16 of the cardiac patients who had in common prominent features of right heart failure, the following characteristic combination was found; an atrial contraction wave of increased duration (0.10 to 0.18 second) and of large amplitude averaging in the different atrial points, recorded in the same individual, 80 to 100 per cent of the total height of the tracing, and abnormal presystolic "a" waves in electrokymograms from the venae cavae and the right diaphragm. This was found in 3 patients with tricuspid valve disease, in 1 instance of rupture of an aneurysm of the sinus of Valsalva into the right ventricle, in 3 patients with old infarction of the ventricular septum, and in 4 patients with constrictive pericarditis. It would appear that in all these instances the particular electrokymographic pattern was caused by mechanical factors compromising right atrial outflow.

PICK

Ostapiuk, F. E.: On Migrating Focus of Stimulation in Idioventricular Rhythm. Klinich. Med. **36/1**: 140, 1958.

In a patient with complete atrioventricular block on the basis of posterior myocardial infarction, the idioventricular rhythm originated in the left bundle branch on 25 occasions during the subsequent 5 years; the rate of this rhythm was slow when inversion of the T wave in leads II and III was greatest. Origin in the right bundle branch was observed on 8 occasions, and the rate was slower when inversion of the T wave in the left precordial leads was greatest. Origin in the common branch was seldom seen.

LEPESCHKIN

Rozenblit, J.: Axis Deviation and Divergence of AQRS and AT in the Wolff-Parkinson-White Syndrome. (Observations in 15 cases). Arch. mal. coeur **51**: 33 (Jan.), 1958.

Of 15 patients with the Wolff-Parkinson-White syndrome, 9 showed Type A (QRS area vector between +38° and +112°, upright QRS in V_1); this type is attributed to pre-excitation of the left ventricle. The axis of T was within normal limits and its deviation from the QRS axis was counterclockwise in this group. Six patients showed type B (QRS axis from -21° to -57°, QS in V_1 in all except 2 cases, which were called "BA"). In this group, which is attributed to pre-excitation of the right ventricle, the axis of T always showed a deviation of 65° to 154° clockwise from the QRS axis as in the pattern of left bundle-branch block.

LEPESCHKIN

Hilmer, W., and Wirth, R.: The Clinical Significance of the Low Voltage Electrocardiogram. Ztschr. Kreislaufforsch. **47**: 194 (Feb.), 1958.

Of 4,000 routine electrocardiograms, 106 showed a maximal voltage of the RS deflection of less than 0.7 millivolt. Of 100 cases studied in detail, 80 had had a systolic blood pressure of less than 80 mm. In 25 patients the ratio of the highest voltage of RS in the limb and the precordial leads was less than 0.35, the lowest value found in 100 normal persons; these patients were said to have absolute low voltage. In this group pulmonary disease was present in 36 per cent, pericardial disease in 24 per cent, myxedema in 12 per cent, myocardial infarction in 8 per cent, and psoriasis in 4 per cent. Seventy five patients had a ratio of more than 0.35, and were said to have absolute relative low voltage; women tended to have higher ratios than men. In this group pulmonary or pleural disease was present in 76 per cent, pericardial disease in 5 per cent, myxedema in 2 per cent, cachexia in 2 per cent, obesity in 9 per cent, and asthenic body build in 8 per cent. A ratio of more than 1 ("paradoxical low voltage") was found in 1 man with extensive myocardial infarction and 2 women with obesity. Various causal factors are discussed in detail in reference to the 3 types of low voltage.

LEPESCHKIN

de Oliveira, J. M., and Zimmerman, H. A.: The Electrocardiogram in Interatrial Septal Defects and Its Correlation with Hemodynamics. Am. Heart J. **55**: 369 (March), 1958.

An electrocardiographic study is presented of 44 patients with interatrial septal defects proved by cardiac catheterization and surgery. It is concluded that RSR′ or RSR′S′ patterns in lead V_1 in this condition do not mean disturbance in conduction of the right branch of the bundle of His but arise from a delay in the activation of the basal portions of the right ventricle and of the higher parts of the interventricular septum because of hypertrophy and dilatation of these structures. This pattern appeared mostly in those anomalies that produced a diastolic overloading of the right ventricle. In uncomplicated interatrial defect the fundamental hemodynamic change is an increase in blood volume-work without significant increase in pressure in the right ventricular chamber. In the author's opinion there is a definite correlation between the morphology of the QRS complex in V_1 and the magnitude of the shunt flow. In the same way, the morphology of the P wave in the right precordial leads bears some relationship to the magnitude of this flow.

SAGALL

Luisada, A. A., Liu, C. K., Aravanis, C., Testelli, M., and Morris, J.: On the Mechanism of Production of the Heart Sounds. Am. Heart J. **55**: 33 (March), 1958.

Phonocardiographic studies of the heart sounds in dogs and man are reported and conclusions regarding the mechanism of the heart sounds are presented. The first heart sound is made of 3 phases: a low-pitched beginning due to myocardial tension; a higher-pitched central phase due to valvular events; and a low-pitched final phase due to vascular phenomena. The central phase contains at least 4 vibrations corresponding to the motion of the heart valves in the following sequence: mitral closure, tricuspid closure, pulmonic opening, and aortic opening. The second heart sound is made of 3 phases: a low-pitched beginning due to eddies preceding the valvular closure; a higher-pitched central phase due to closure of the semilunar valves; and a low-pitched final phase due to final vibrations plus opening of the A-V valves. The central and final phases correspond first to the closure of the semilunar valves and, then, to the opening of the A-V

valves in this order; aortic closure, pulmonic closure, tricuspid opening, and mitral opening. Rapid filling of the ventricle is usually nonsimultaneous in this order: rapid filling of right ventricle, rapid filling of left ventricle. The time intervals for the various phases in large dogs are given and measurements taken in phonocardiograms of normal persons recorded in the same manner indicate that similar figures can be used in man.

SAGALL

Soloff, L. A., and Zatuchni, J.: Relationship of the P Wave to Left Atrial Volume in Rheumatic Heart Disease with Mitral Stenosis. Am. J. M. Sc. **235**: 290 (March), 1958.

The P waves of the electrocardiograms of 20 patients with rheumatic heart disease and mitral stenosis were studied with reference to abnormalities in contour in relation to the volume of the left atrium. The combined technic of cardiac catheterization and biplane stereoscopic angiocardiography was employed for evaluation of intracardiac volumes and flow velocities. Notching, amplitude, or duration of the P wave could not be correlated with the degree of left atrial enlargement demonstrated. Notching of the P wave was commonly observed while high amplitude was the least frequent abnormality in patients with mitral stenosis. For any given amplitude of P wave, the left atrial volume varied greatly. The electric axis of the P wave was usually semivertical, occasionally vertical, and rarely horizontal. In lead V_1, the qR complex was unrelated to left atrial enlargement but was associated with cardiac hypertrophy, right atrial enlargement, and pulmonary hypertension. The enlargement of left atrium showed a tendency to rightward deviation of the P wave but was best correlated with rightward deviation of QRS.

SHUMAN

Duboucher, G.: The U Wave and Its Mechanographic Component (Clinical Study). Arch. mal. coeur **51**: 22 (Jan.), 1958.

In patients with sinus arrhythmia, atrial extrasystoles or atrial fibrillation, the U wave usually shows greater voltage after long diastolic pauses. This applies to positive as well as to negative U waves. As the configuration of QRS remains unchanged, the U-wave changes must be considered as primary; they are attributed to accumulation of blood in the atria and the resulting greater diastolic distention of the ventricle. The T wave often shows changes opposite to those of the U wave. In cases that show no change of U, this wave is usually very small. In some patients with atrioventricular dissociation due to complete block or to sinus bradycardia with nodal escape rhythm, the U wave was taller in ventricular complexes in which the P wave was superimposed on the QRS complex or S-T segment than in those preceded by the P wave, although the preceding diastolic pause remained unchanged. The only explanation applicable to these cases is that coincidence of atrial and ventricular contraction prevents proper emptying of the atria, and the filling of the ventricle at the beginning of the following diastole is more forceful. In 1 patient with pulsus alternans the U wave also appeared to show alternation. The conclusion is made that the U wave must result at least in part from the mechanical effect of ventricular filling.

LEPESCHKIN

Bengtsson, E.: Electrocardiographic Studies in Patients with Abnormalities in Serial Examinations with Standard Leads during Acute Infectious Diseases. I. Occurrence of Abnormalities in the ST-T Complex of Chest Leads in Resting Electrocardiograms Suggestive of Localized Myocardial Lesions. Acta med. scandinav. **159**: 395 (Dec. 16), 1957.

In 217 consecutive patients, admitted to the Contagious Diseases Hospital, Stockholm, for various acute infectious diseases, standard, unipolar extremity and chest leads were taken concurrently once weekly for at least 3 to 5 weeks. Electrocardiographic signs suggestive of myocardial lesions were observed in 11 patients. In 4 of these, abnormal changes were demonstrated only with chest leads, the extremity leads either being normal or showing only slight or ambiguous changes. At the same hospital, abnormal electrocardiographic changes were observed to occur in the serial standard leads taken routinely in 210 out of 2,310 patients with acute infectious diseases. Most of the abnormalities consisted of T-wave changes. Chest leads were also obtained on these patients. In most instances it was possible to localize the electrocardiographic changes in this series to one or more leads corresponding to the right ventricle, apical region, or left ventricle. In children, changes were more frequently localized to the right ventricle, while signs of left ventricular involvement were more frequent in adults. Chest leads showed the most pronounced changes and were diagnostically significant more often than the unipolar extremity or standard leads. The author believes this study demonstrates that a full set of chest leads greatly enhances the possibility of making a diagnosis of myocarditis.

BROTHERS

Bengtsson, E.: Electrocardiographic Studies in Patients with Abnormalities in Serial Examinations with Standard Leads during Acute Infectious Diseases. II. Chest and Extremity Leads During and After Exercise. Acta med. scandinav. **159**: 411 (Dec. 16), 1957.

In a group of 98 patients with a variety of acute infectious diseases, changes had taken place in their resting electrocardiograms. After the resting electrocardiograms of these patients had returned to a normal, or almost normal, pattern, exercise electrocardiograms were done and were interpreted as being abnormal in more than 40 per cent. In the majority of patients, the principal change consisted in abnormalities of the ST-T complex. Disturbances of rhythm, chiefly extrasystoles, were also common and were encountered in adults more frequently than in children. Patients who had earlier shown disturbances of rhythm on the resting electrocardiograms presented abnormal exercise electrocardiograms to a greater extent than those with changes mainly in the ST-T complex or the P-Q interval. The changes sometimes appeared both during and after exercise but often only during exercise. Chest leads taken at 3 to 4 minutes after exercise disclosed abnormal findings in more than 40 per cent of all the cases investigated and by comparison with the standard leads and lead aV_R, were much more valuable in detecting electrocardiographic abnormalities. Chest lead abnormalities occurred more often in children than in adults. As in an earlier investigation with resting electrocardiograms, changes corresponding to the right ventricle were seen more frequently in children than in adults, whereas changes corresponding to the left ventricle were more common in adults than in children.

BROTHERS

Stein, G.: On the Differential Diagnosis of Bilateral Bundle Branch Block. Ztschr. Kreislaufforsch. **47**: 140 (Feb.), 1958.

In 1 patient, each series of 2 to 3 sinus beats with a P-R interval of 0.33 second and right bundle-branch block (Type V) was terminated by a blocked P wave; the following complex always showed a P-R of 0.22-0.24 second and a "paradoxical" left bundle-branch block. To explain this pattern, the assumption is made that the right bundle-branch shows a variable conduction disturbance dependent on the preceding pause, while the left branch shows a considerable conduction delay independent of the preceding pause. The diagnosis of a bilateral bundle-branch block can accordingly be made only if alternation between right and left bundle-branch block is always accompanied by a corresponding change in the P-R interval. In the case of 1 patient with such alternation and complete atrioventricular block, and of 2 patients with delayed intrinsicoid deflection in right as well as left precordial leads, this diagnosis could not be made with certainty. These patterns can result also from unilateral block combined with a conduction disturbance in the atrioventricular node, peri-infarction block, left ventricular hypertrophy, or left intraventricular block.

LEPESCHKIN

Heidel, W., and Richter, W.: Significance of Low Voltage in the Electrocardiogram. Ztschr. Kreislaufforsch. **47**: 271 (March), 1958

Of 4,320 patients subjected to electrocardiographic study during a single year, 5.9 per cent showed a QRS amplitude less than 0.5 mV. in the limb leads. The average age in this group was significantly higher. Sixty-five per cent had pulmonary emphysema, 5 per cent hepatic cirrhosis or neoplasms, 14 per cent heart disease, and 6.5 per cent peripheral edema. Low voltage in precordial leads was found in only 9 per cent. Other electrocardiographic abnormalities were found in 48 per cent. The incidence of low voltage in pulmonary emphysema was 14 per cent, whereas in marked emphysema it was 39 per cent; the higher incidence in emphysema is statistically significant. The incidence in malignant neoplasms was 13 per cent, in hepatic cirrhosis 14 per cent, and in adrenal insufficiency 10 per cent; in these groups the increased incidence was not significant statistically. In myxedema the incidence was 47 per cent. In patients with hepatic cirrhosis there was no relation between the incidence of low voltage and that of increased serum globulins. The results emphasize the significance of extracardiac factors in the genesis of low voltage.

LEPESCHKIN

Sachs, D.: Esophageal Phonocardiography in the Registration of Diastolic Murmurs in Atrial Septal Defect as a Result of Increased Right Atrial Load. Ztschr. Kreislaufforsch. **47**: 221 (March), 1958.

Of 12 patients with atrial septal defects, 8 showed middiastolic or presystolic murmurs only in the esophageal phonocardiogram, registered through a catheter having a window with a rubber membrane, but not in the precordial phonocardiogram. These murmurs were attributed to a relative tricuspid stenosis caused by the increased blood flow through this orifice. In 2 patients isolated early diastolic murmurs appeared in the esophageal as well as the precordial phonocardiogram.

LEPESCHKIN

Bender, F., and Seifert, H. H.: Diagnostic Use of Photo-Cell Catheter. Ztschr. Kreislaufforsch. 47: 260 (March), 1958.

A light source having a wave length of 620 mμ and a small selenium photocell are placed at the tip of a no.-9 cardiac catheter, separated by a slit accessible to intracardiac blood. Blood samples used in calibration of the catheter can be taken through an opening in the side of the catheter next to the photocell. Intracardiac pressures can also be registered through this opening. The entire assembly is only slightly larger than the diameter of the catheter, and is now manufactured by the Rüsch Company, Rommelshausen/Stuttgart. The advantage of the method is that the oxygen saturation in any position of the catheter can be registered immediately, without loss of blood. In 1 patient a sudden change in oxygen saturation at the boundary between right atrium and superior vena cava could be demonstrated repeatedly. In this way the site of a left-to-right shunt can be located much more accurately than with other methods.

LEPESCHKIN

Kenner, T., and Alth, G.: On Evaluation of Electrokymographic Curves. Ztschr. Kreislaufforsch. 47: 15 (Jan.), 1958.

Synchronized registration of curves from many points of the ventricular border shows that each electrokymogram is the resultant of changes in volume, configuration, and pendular movements. The latter are caused by systolic movement of the ventricular apex into a position perpendicular to the valvular plane, and are least pronounced at the base of the heart. Separation of 2 of these components is possible if one of them can be determined approximately. The time of appearance of different points on the resultant curve does not coincide with corresponding points on the component curves. The isometric period of contraction can therefore not be measured accurately on either the ventricular or the aortic curve, but the beginning of the rapid rise of ventricular pressure can be determined in most ventricular curves.

LEPESCHKIN

Pordtheine, H.: The Vectorcardiographic Pattern of Small and Large Anterior Myocardial Infarction. Arch. Kreislaufforsch. **28**: 56 (Feb.), 1958.

Study of the cube-system vectorcardiogram in 14 patients with anterior infarction and a QRS duration of 0.10 second or less showed that anteroseptal infarction was characterized by indentation of the Q portion of the vector loop, and anterolateral infarction by indentation of the R portion of the loop and extrusion of the S portion, while large anterior infarction combined both these characteristics. Absence of the R wave in leads V_1-V_2 in left ventricular hypertrophy was usually accompanied by a smooth QRS loop while the same pattern in anteroseptal infarction usually was accompanied by typical indentation in the Q portion of the loop. If infarction is accompanied by considerable cardiac enlargement the area of infarction may no longer face any of the standard precordial leads, which show only low voltage of R, but the vector loop still shows typical indentation in the Q portion; in the limb leads these changes may appear only as a notch preceding R. Fresh infarction is characterized by displacement of the S-T vectors forward, downward and to the left, while in the healing phase T vectors show displacement backward, upward, and to the right.

LEPESCHKIN

Abel, H.: The Angle between the Ventricular Gradient and the Vector of QRS Area. Ztschr. Kreislaufforsch. **47**: 135 (Feb.), 1958.

Detailed serial studies in 2 patients with anterior myocardial infarction showed deviation of the gradient to the right of the QRS axis, while in 3 patients with posterior infarction it deviated to the left. One patient with an apparently normal resting electrocardiogram showed deviation of the gradient 28° to the right of QRS, and this was considered to indicate left ventricular ischemia.

LEPESCHKIN

ENDOCARDITIS, MYOCARDITIS, AND PERICARDITIS

Wedgewood, J.: Prognosis in Subacute Bacterial Endocarditis. Lancet **2**: 122 (Nov. 9), 1957.

Twenty-nine patients with subacute bacterial endocarditis were treated with penicillin from 1946 to 1954. Eleven (38 per cent) died, 11 (38 per cent) were worse than before their illness, and only 7 (24 per cent) did not appear to have deteriorated. Eight patients died of congestive heart failure within 2 years of the start of treatment. The prognosis was not affected by the organism, but the site of valve disease was important. Ten patients had predominant aortic incompetence. Six of these died from heart failure, and the other 4 were worse than before their illness. In general, the mortality tended to be higher in the patients who had been ill the longest. Congestive heart failure, cardiac enlargement, and atrial fibrillation were associated with a poor prognosis.

KURLAND

Dines, D. E., Edwards, J. E., and Burchell, H. B.: Myocardial Atrophy in Constrictive Pericarditis. Proc. Staff Meet., Mayo Clin. **33**: 93 (Feb. 19), 1958.

In order to determine whether myocardial atrophy actually occurred in constrictive pericarditis, the authors used micrometer measurements of the diameter of the myocardial fibers. Eleven cases of constrictive pericarditis were studied in regard to the thickness of their myocardial fibers. These measurements were then compared to those obtained in normal hearts and also cases of chronic exudative pericarditis and chronic pericardial effusion. In each of the 11 hearts from patients with chronic constrictive pericarditis, myocardial atrophy was seen. This atrophy appeared uniformly in both ventricles. In those cases of exudative pericarditis, atrophy was only seen in the area of myocardium adjacent to the inflammatory process in the epicardium. In 2 cases of chronic pericardial effusion, there was evidence of myocardial atrophy similar to the atrophy in constrictive pericarditis possibly due to the long duration of the compression.

KRAUSE

Koulumies, R., and Heinivaara, O.: Observations on Penicillin Therapy in Cardiovascular Syphilis. Acta med. scandinav. **159**: 453 (Dec. 28), 1957.

One hundred and twelve patients with cardiovascular syphilis were treated with penicillin only. No fatal complications definitely attributable to penicillin occurred. A follow-up study of 54 patients who received their therapy 5 or more years earlier, disclosed that only 23 (42.6 per cent) were living 5 years after treatment. The prognosis in this group as well as in the full series was significantly better in women. The total penicillin dosage did not appear to influence the prognosis, for there was no demonstrable difference in this respect between those receiving less than 10 million units and those receiving 10 million units or more. Grouped on the basis of functional capacity according to the classification of the New York Heart Association, it was clearly evident that the greater the functional impairment at the time of treatment, the poorer was the prognosis. Of the patients falling into Class I and II, 60.6 per cent were living 5 years later, whereas for those falling into Class III and IV only 9.0 per cent survived 5 years. Four of the 23 patients surviving for 5 years, died during the sixth year leaving 19 available for a follow-up examination, to which 14 responded. Thirteen of these were originally designated as being in functional class I or II. Ten patients were working. All had been using some form of cardiac medication. Although this series of patients does not definitely demonstrate the superiority of penicillin treatment over earlier methods, it has the practical advantage of easy administration and the complications ascribable to the treatment are so rare that penicillin therapy is to be considered the treatment of choice in cardiovascular syphilis.

BROTHERS

Dormer, A. E.: Bacterial Endocarditis. Survey of Patients Treated Between 1945 and 1956. Brit. M. J. **1**: 63 (Jan. 11), 1958.

The authors discuss the treatment of bacterial endocarditis from the year 1945 to the end of 1956. A total of 82 patients were included in the survey. The immediate mortality was about 27 per cent. A delay in diagnosis was demonstrated in a high percentage of patients and this was particularly true when features less typical of endocarditis dominated the clinical course. Precipitating factors were also investigated, and the extraction of infected teeth without antibiotic coverage was responsible for the infection in 11 patients. As reported in the literature, streptococcus viridans was by far the most common organism found. When blood cultures were positive, it was usually the first blood culture that helped identify the organism. Fifteen of the group were diagnosed as having 2 attacks of endocarditis apparently due to inadequate antibiotic treatment. When the infections seemed resistant to penicillin, increased dosage of the drug and the addition of streptomycin usually proved to be successful. The disease has its greatest mortality and is more often missed among the older age groups.

KRAUSE

HYPERTENSION

Poutasse, E. F., and Dustan, H.: Arteriosclerosis and Renal Hypertension. J. A. M. A. **165**: 1521 (Nov. 23), 1957.

The fact that experimental hypertension can be produced by partial occlusion of a renal artery and the demonstration of the renal pressor system led the authors to study certain hypertensive patients by means of aortography. This method of study was not used routinely but was performed on 4 classes of hypertensive patients: (1) those with unexplained disparity of the size or function of the kidneys by intravenous urography; (2) those young patients who do not seem to have essential hypertension; (3) those elderly hypertensive patients who suddenly develop accelerated or malignant forms of the di-

case; (4) those individuals of any age with long-standing essential hypertension when the disease abruptly becomes more serious. One hundred four patients were studied and 30 were found to have focal renal artery disease. Nineteen of these 30 were subjected to various surgical procedures, ranging from endarterectomy through renal artery grafting to nephrectomy. Nephrectomy is the choice when there is unilateral disease with atrophy and reduced function of the involved kidney. Of the 19 operated on, 5 have normal blood pressure, 2 have had reversal of malignant hypertensive syndrome even though they still have hypertension. These have been followed more than a year. In patients followed less than 1 year, blood pressure returned to normal in 6. Death has occurred in 2 patients postoperatively (1 from renal failure and the other from hemorrhage).

KITCHELL

Lumb, B. R. B., and Greshman, G. A.: Phaeochromocytoma of the Urinary Bladder. Lancet **1**: 81 (Jan. 11), 1958.

This is the third recorded report of a pheochromocytoma of the urinary bladder. The tumor produced pressor amines and gave rise to a recognizable striking clinical picture. Typical attacks consisted of palpitations, headache, pallor, and sweating commencing as soon as the bladder was emptied, lasting a few minutes, occurring only in the summer. Remission occurred from menarche at 15 to age 41. Urine contained 0.8 mg. norepinephrine per ml. When cystoscopy revealed a bladder tumor, operation was performed. The tumor contained epinephrine and norepinephrine. The urinary output of catechol fell postoperatively, but the blood pressure remained 190/100 mm. Hg although the patient was asymptomatic.

KURLAND

Arora, R. B., Singh, K. P., Das, P. K., and Mistry, P. N.: Prolonged Hypotensive Effect of the Essential Oil of Nardostachys Jatamansi. Arch. int. pharmacodyn. **113**: 367 (Jan.), 1958.

A solution of the essential oil of Nardostachys jatamansi in Tween 80, beta alcohol, and propylene glycol was injected in the femoral vein of dogs. A prolonged and marked hypotensive effect was produced. In moderate doses the drug did not cause electrocardiographic changes; it had a negative inotropic effect; it did not block ganglionic transmission; it had some adrenolytic action; it did not depress the vasomotor center, but it blocked the proprioceptive blood pressure-regulating reflexes. Although these effects may contribute to the hypotensive action of the drug, it appears that this is primarily due to a direct peripheral vasodilator effect. The "therapeutic ratio" of this drug is very high; although there are no controlled clinical observations, clinical trial of this preparation in selected cases of hypertension and of peripheral vascular diseases appears justified.

CALABRESI

Hazard, R., Hazard, J., and Mouille, P.: Inversion of Hypertensive Effects of Epinephrine and Norepinephrine in the Rabbit by Some Adrenolytic Agents. Arch. int. pharmacodyn. **113**: 136 (Dec.), 1957.

In rabbits under urethane anesthesia and artificial respiration, after bilateral vagotomy and intravenous atropine sulfate, intravenous injections of epinephrine or norepinephrine in adequate dosage caused a reproducible hypertensive effect. To study the influence of adrenolytic drugs on this hypertensive effect, gradually increasing doses of the following agents were administered by intravenous injections: Prosympal and Benodaine (both benzodioxane derivatives); Priscol and Regitine (imidazoline derivatives); Dibenzyline; Ilidar; Dihydroergotamine. Each animal was tested with only 1 of these drugs. Previous investigators have found it difficult to obtain blockade or reversal of hypertension, particularly after norepinephrine. In these experiments 3 different results have been noted, varying with the inhibiting agent used and with its dosage: blockade of the hypertensive effect; diphasic reaction (hypotension followed by hypertension); reversal of the hypertensive response. No qualitative difference has been noted in the influence of these drugs on the hypertensive response to epinephrine or norepinephrine, although frequently higher doses were necessary to elicit the inhibitory effect when norepinephrine was used as the hypertensive agent.

CALABRESI

Lühr, K.: Observations on the Regulation of Heart Output and Blood Pressure in Arterial Hypertension. Ztschr. Kreislaufforsch. **47**: 60 (Jan.), 1958.

Determinations of cardiac stroke volume according to Wezler and Böger were carried out in 2,833 patients; of 1,355 patients with hypertension 25 per cent showed a stroke volume exceeding 100 ml. Persons without hypertension showed such values in only 7 per cent. In 3 patients without hypertension who showed an elevated stroke volume and increased duration of the resonant oscillation of the arterial system,

arterial hypertension developed later. It is concluded that an increase in stroke volume is the cause of hypertension in some of the patients.

LEPESCHKIN

Polak, F., and Mencik, Z.: Influence of Digestive Activity on the Blood Pressure Regulation of Patients with Hypertension under the Influence of Reserpin and Phthalazine Bodies. Ztschr. Kreislaufforsch. **47**: 97 (Feb.), 1958.

One hour after meals the blood pressure shows a decrease parallel in its magnitude to the initial pressure level; this decrease does not appear after ingestion of barium sulfate and must therefore be attributed to digestive activity. It is caused by a decrease in the peripheral resistance, while the heart output remains essentially unchanged. It does not appear after previous medication with nepresol, since this drug acts primarily on the peripheral resistance. On the other hand, it is not influenced by previous medication with Serpasil, since this substance acts primarily on the cardiac output.

LEPESCHKIN

Semenova, K. N., and Belyaeva, Z. V.: Comparative Data on the Therapeutic Efficacy of Sleep-Induced Inhibitions in Hypertension and Gastro-duodenal Ulcer. Klinich. Med. **36**/2: 33, 1958.

Treatment with sleep induced by means of barbituates and conditioned reflexes in 73 patients with ulcers caused improvement immediately in 37 and after 4 to 6 months in 63 persons. The same treatment in 40 patients with hypertension caused improvement immediately in 22 and after 4 to 6 months in 9 persons. Basal metabolism and blood sugar were usually more normal after treatment. Patients with ulcers usually showed predominantly inversion of the skin temperature reaction to heat, while those with hypertension showed predominantly inversion of the blood pressure reaction to cold. After treatment the reaction least affected before treatment usually became more normal.

LEPESCHKIN

PATHOLOGY

Truex, R. C., and Bishof, J. K.: Conduction System in Human Hearts with Interventricular Septal Defects. J. Thoracic Surg. **35**: 421 (April), 1958.

The authors report detailed anatomic studies of the specialized conduction tissues in 15 human hearts with high interventricular defects. In all cases there were additional cardiac anomalies, but no cardiac arrhythmias. Ten specimens were studied in microscopic serial sections, and 5 were studied grossly with the aid of a dissection microscope. The conducting tissues were readily identified by Masson stain in the microscopic sections, and by their pale appearance in the gross specimens. In 12 of the 15 specimens the common bundle as well as the left and right bundle branches were found to be in the postero-inferior margin of the septal defect. This corroborates the presumed location previously reported by Kirklin. In 7 of 10 microscopic specimens early rami (Mahaim's fibers) were demonstrated. These arise above the bifurcation of the bundle and pass directly into the septal myocardium. Another unexpected finding was the presence of accessory pathways (bundles of Kent) connecting the common bundle above the fibrous ring with the septal myocardium below. The latter 2 accessory pathways may become very important in cases where the common bundle is injured in the course of surgical repair. Hemorrhage of unexplained origin was found in the conducting system in 6 cases.

ENSELBERG

Lev, M., Benjamin, J. E., and White, P. D.: A Histopathologic Study of the Conduction System in a Case of Complete Heart Block of 42 Years' Duration. Am. Heart J. **55**: 198 (Feb.), 1958.

The case of a 57-year-old woman with known complete heart block of at least 42 years' duration is presented with a detailed histopathologic study of the conduction system, the atria, and the ventricles. The atrioventricular node was found to be absent or fibrosed and there was a complete lack of connection between the atrial musculature and the bundle of His. The atrial musculature was malformed and exhibited marked fibrosis, fatty infiltration, and calcification with areas of absent or replaced muscles. It was suggested that the atrial changes were due to a congenital malformation and that the patient had either congenital heart block or congenital heart disease with acquired heart block.

SAGALL

Peckholz, I., Giepel, M., and Kupfer, M.: Problems in the Pathology of Isthmic Aortic Stenosis. Ztschr. Kreislaufforsch. **47**: 2 (Jan.), 1958.

In 20 patients with aortic isthmic stenosis and 50 normal individuals of a comparable age, aortic diameter and thickness of the aortic wall showed considerable individual variability in normal persons, so that absolute measurements could not be used in the diagnosis of stenosis. This could be made definitely if the ratio of the diameter of

the aortic ostium to that of the narrowest region of the aorta exceeded 1:0.40, for in all normal individuals the ratio was smaller. Some patients with stenosis had values between 1:0.40 and 1:0.60, but in these patients the difference between the ratios at the isthmus and the thoracic aorta was greater than 0.30. Hypertrophy or atrophy of the aortic wall or structural differences between the aorta proximal and distal from the point of stenosis could not be found, except in 1 patient with congenital aortic hypoplasia.

LEPESCHKIN

PHARMACOLOGY

Papp, C., and Smith, K. S.: Urea, The Forgotten Diuretic. Brit. M. J. **2**: 906 (Oct. 19), 1957.

Urea, once considered a satisfactory diuretic, is rarely used for this purpose today. In an attempt to re-evaluate this substance, the authors studied for varying periods of time ranging from 2½ weeks to 7 years, 17 patients with chronic right ventricular failure and ascites. These patients were now refractory to mercurial diuretics. Fifteen grams of urea in 57 ml. of water or grapefruit juice were used 3 times daily after meals. There were 3 therapeutic failures: 1 patient had complete lack of response to the drug, 1 patient died before sufficient time elapsed for proper evaluation, and 1 refused to take further medication after 1 week. Urea as a diuretic does seem to have a place in the therapy of chronic congestive failure with edema. In 50 per cent of the patients a negative fluid balance was changed to a positive one. In those instances in which a negative fluid balance persisted, it was at least reduced in magnitude. As a matter of fact, urea may convert an intractable case of congestive heart failure to a controlled case. Such patients have been able to continue with restricted physical activities for several years when the initial situation seemed hopeless. The chief disadvantage is that the drug is unpalatable and may cause vomiting and gastrointestinal irritation when administered in the required dose. Furthermore, although the blood urea nitrogen may rise with the administration of the drug, the presence of uremia does not contraindicate its use.

KRAUSE

Lubner, R. S., and Kallman, H.: Treatment of Digitalis Toxicity by Chelation of Serum Calcium. Am. J. M. Sc. **234**: 136 (Aug.), 1957.

Calcium and digitalis have been shown to have synergistic effects in enhancing cardiac irritability mediated by their influences upon cellular ionic permeability. It is probable that both inhibit the influx of potassium into the myocardial cells. The binding of serum calcium by ethylenediamine tetraacetic acid (EDTA) was found to terminate promptly the arrhythmias due to digitalis toxicity in 3 patients. EDTA did not lower circulating calcium levels but rapidly sequestered ionized calcium in a physiologically inert form. It was excreted in the urine with bound calcium over a 48-hour period. Both atrial and ventricular ectopic rhythms caused by digitalis were abolished. In 2 other patients, prior administration of sodium or magnesium salts of EDTA in doses of 600 mg. in 250 ml. of 5 per cent glucose in water intravenously over 15 to 30 minutes offered certain advantages over potassium therapy in treating digitalis toxicity. The effect of potassium is delayed and in large doses orally it may be poorly tolerated. Arrhythmias due to digitalis toxicity should be promptly corrected because of the possible development of fatal ventricular fibrillation and because heart failure is aggravated by the arrhythmias. The use of EDTA affords a means of rapidly overcoming digitalis toxicity.

SHUMAN

Burn, J. H., and Rand, M. J.: Action of Nicotine on the Heart. Brit. M. J. **1**: 137 (Jan. 18), 1958.

The authors studied the effect of nicotine on the atria of rabbits. Since nicotine is a ganglionic stimulant, it has an inhibitory action on the rate of the isolated heart. However, it also has a stimulant action that can be demonstrated when the atria are dissected from other tissues and suspended in a bath that contains atropine to exclude the inhibition. The stimulant action is probably due to the fact that nicotine releases norepinephrine and epinephrine from stores within the heart. When the rabbits were prepared with reserpine, the atrial depots of epinephrine and norepinephrine were depleted. The atria prepared in this way were not stimulated by the action of nicotine. The cardiac stores of epinephrine and norepinephrine normally exerted some effect and accelerated the spontaneous rate of the heart. The mean rate of atria from animals treated with reserpine was 112 and that of isolated atria from control animals was 142 per minute. If this data can be transferred to human subjects, smoking may liberate norepinephrine and epinephrine from cardiac depots, and thus produce acceleration and exaggerate ventricular arrhythmias. On this basis, smoking may be contraindicated in patients who have cardiac abnormalities.

KRAUSE

Angarskaya, M. A. Khadzhai, Y. I., Kolesnikov, D. G., Prokopenko, A. P., Dubinsky, A. A., and Shubov, M. I.: Daucarin - A New Soviet Drug for the Treatment of Coronary Insufficiency. Klinich. Med. **36**/1: 29, 1958.

Daucarin (an alcoholic extract of carrot seeds) definitely decreases smooth muscle tonus in animals. It was tested in 88 patients with angina pectoris in an oral dose of 20 mg. 3 to 5 times daily for 1 to 3 weeks, after a control period of 1 week. Sixty-six per cent of the patients showed definite improvement, 16 per cent questionable improvement, and 18 per cent no change. The improvement was greatest in persons with hypertension. No unpleasant side effects were observed.

LEPESCHKIN

Zamboni, P.: The Capillary Resistance in Rats Treated with Reserpine. Arch. int. pharmacodyn. **113**: 203 (Dec.), 1957.

The resistance of the capillary vessels of the skin to negative pressure was studied in female rats treated with intraperitoneal injections of reserpine in single doses of 1 or 3 mg. per Kg. of body weight. In another series of experiments the drug was administered for 10 or 21 days, daily or on alternate days. Adequate series of controls were also studied. These treatments caused marked depletion of platelet 5-hydroxytryptamine, but did not produce decrease in the capillary resistance. These experiments complement observations of other investigators, indicating that platelet 5-hydroxytryptamine depletion does not prolong the bleeding time; they do not support the theory that 5-hydroxytryptamine influences hemostasis.

CALABRESI

Rand, M. J., and Walker, J. M.: A Comparison of Antifibrillatory Drugs in the Heart-Lung Preparation, Brit. J. Pharmacol. **13**: 107 (March), 1958.

Quinidine, amethocaine, Trasentin, and atropine were tested for the ability of each to stop atrial fibrillation produced in a dog heart-lung preparation by stimulating the right atrium in the presence of acetyl choline and to decrease the maximum rate at which the rabbit atria would respond to electric stimuli. Atropine appeared to act by inhibiting acetyl choline, but the action of amethocaine and Trasentin was mainly quinidine-like. Amethocaine potentiated the effect of acetyl choline on the atria while both quinidine and Trasentin had some atropine-like influence.

ROGERS

Goodkind, M. J., Harvey, R. M., and Richards, D. W.: Use of Chlorothiazide in the Treatment of Edema. Am. J. M. Sc. **235**: 164 (Feb.), 1958.

The diuretic action of chlorothiazide was examined in 13 patients with edema of various etiologies including 10 with cardiac failure, 2 with cirrhosis, and 1 with nephrosis. Observations on the weight curves and serum electrolytes were conducted before and during the course of treatment with this agent. Favorable effects were noted in 7 of the 10 cardiac patients and in the 2 cirrhotic patients. Several patients resistant to other diuretic agents responded well to chlorothiazide. A transient and asymptomatic lowering of serum potassium levels developed in 5 cases during treatment with this agent. The nephrotic patient was resistant to all therapy. Chlorothiazide has been employed on a weekly schedule of intermittent therapy, 4 days on and 3 days off.

SHUMAN

Hunt, J. C., Anderson, M. W., and Hanlon, D. G.: Hemorrhagic Diathesis Related to Quinidine Therapy. Proc. Staff Meet., Mayo Clin. **33**: 87 (Feb. 19), 1958.

The authors report 4 cases of purpura related to quinidine toxicity. The hemorrhagic picture may vary from one of premonitory symptoms with scattered petechiae and ecchymoses to that of sudden onset of bleeding from multiple sites and systems. Usually most patients have had previous exposure to quinidine, but an occasional case of purpura has been observed in patients not aware of previous quinidine therapy. The diagnosis is made clinically and requires a high index of suspicion. The hematologic findings are those of acute thrombocytopenia. On rare occasions a fatal case has been reported. Usually when quinidine therapy is discontinued after the diagnosis is correctly made, the prognosis for recovery is good.

KRAUSE

Maengwyn-Davies, G. D., Walz, D. T., and Koppanyi, T.: Role of Buffer Mechanisms in Sympathetic Drug Action. Arch. int. pharmacodyn. **113**: 427 (Jan.), 1958.

The hypothesis that the potentiation of sympathetic neurohormones by ganglionic-blocking agents is due to the elimination of the aortic arch and carotid sinus baroreceptors has been tested in atropinized dogs in sodium pentotal anesthesia; the carotid sinuses and the ganglia nodosa had been removed bilaterally, thereby eliminating also the afferent fibers from the aortic arch. Hexamethonium potentiation of epinephrine or norepinephrine was still obtained. Epinephrine

reversal by dibenamine was prevented by hexamethonium, but was not influenced by removal of the baro-and chemoreceptors. The relationship between the potentiating effect of hexamethonium and the results of sympathectomy and of in vitro oxidase inhibitors, and also the possible mechanisms of action of the ganglionic-blocking agent are briefly discussed.

CALABRESI

Elkim, M., Rosenberg, S. Z., and Braun, K.: Effect of Acetylcholine on the Pulmonary Artery Pressure in Anesthetized Dogs. Arch. int. pharmacodyn. **113**: 169 (Dec.), 1957.

In order to study the site and mechanism of action of the drug on the pulmonary artery pressure, the hemodynamic effects of injections of acetylcholine hydrochloride at various sites and in doses varying from 1 to 500 μg. per Kg. of body weight have been studied in anesthetized dogs. The pulmonary artery and left atrial pressures have been measured by means of right and left heart catheterization; catheters have also been passed into the abdominal aorta and inferior vena cava via the femoral vessels. The injection in the pulmonary artery causes a rise in pulmonary artery pressure and a fall in systemic arterial pressure. Aminophylline, in doses insufficient to affect the systemic arterial pressure, diminishes, but does not abolish, the rise in pulmonary pressure. This effect is interpreted as due to the bronchodilator effect of aminophylline; since large doses of this drug do not abolish the pulmonary artery hypertensive effect of acetylcholine, it is concluded that bronchospasm is only 1 of the factors responsible for the rise in pulmonary artery pressure. Following injection in the pulmonary artery, there is no significant change in left atrial pressure; the systemic arterial pressure falls, mainly due to the cardiac effect of the drug. Injection in the inferior vena cava has similar effects. Injection into the aorta causes a drop in the systemic pressure, due to peripheral vasoconstriction, and a late rise in pulmonary artery pressure, apparently secondary to an increase in venous return and in pulmonary artery flow. Injection in the portal vein has no effect on the systemic pressure and an insignificant effect on the pulmonary artery pressure, presumably because of the rapid enzymatic inactivation of the acetylcholine in the liver.

CALABRESI

O'Meara, D., Shepherd, D. M., and West, G. B.: The Vasodilator Action of Glucose Nitrates. Arch. int. pharmacodyn. **113**: 432 (Jan.), 1958.

The effect of a series of glucose nitrates on the blood pressure has been studied in dogs under sodium pentobarbitone anesthesia. The drugs were given by intravenous injections or by mouth. Mono- or dinitrates were found to be inactive; compounds containing 3 or 4 nitrate groups possessed depressor activity comparable with that of erythritol tetranitrate. Data are given on the structure-activity relationship of these compounds. The need for further studies is indicated. No correlation has been found between the depressor effect and the amount of nitrate ion released in vitro by alkaline hydrolysis; the formation of nitrates in vivo has not been studied yet; it is known, however, that other vasodilator organic nitrates that liberate large amounts of nitrite on alkaline hydrolysis in vitro have very little effect on the blood nitrite level of dogs.

CALABRESI

Beck, I. T., and Beck, M.: The Anti-fibrillatory Action of 2-Pentene 1-4-Olide (Alpha-beta Unsaturated Angelica Lactone) on the Electrically Induced Ventricular Fibrillation of the Cat's Heart. Arch. int. pharmacodyn. **113**: 400 (Jan.), 1958.

Ventricular fibrillation was induced in cats under chloralose anesthesia and artificial respiration by direct electric stimulation. After 5 minutes of cardiac massage, 2-pentene 1-4-olide (alpha-beta unsaturated angelica lactone) was administered by intravenous or intracardiac injections in doses of 200 mg. per Kg. of body weight, with reversion to normal rhythm within 5 minutes or less. In 4 cats the same dose was also given before adequate electric stimulation, and either prevented or decreased the duration of ventricular fibrillation. In previous investigations it was seen that the drug may reverse ventricular arrhythmia due to digitalis or to barium chloride. It is suggested that this lactone be tested clinically for treatment of premature beats and of atrial or ventricular fibrillation.

CALABRESI

Prasad, B. N.: Role of Prednisone in Acute Pulmonary Oedema. Arch. int. pharmacodyn. **114**: 146 (March), 1958.

Acute pulmonary edema was produced in guinea pigs by intravenous injection of 1 per cent chloropicrin in hydroalcoholic base. The protective effect of various drugs, including phenergan, alcohol aerosol, morphine sulfate, and ACTH is reported. At the doses used ACTH protected 6 out of 10 animals; all the other drugs were less effective; cortisone and hydrocortisone were of little help. Prednisone protected all the animals tested, both when chloropicrin was given in LD_{50} and in LD_{100} dose. The possible mechanism of action of the drug is briefly discussed.

CALABRESI

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.
Telephone Gramercy 7-9170

NEW GRANTS BRING 1958-59 RESEARCH SUPPORT TO TOTAL OF $3,063,604

Under the national research support program of the American Heart Association and its affiliates, grants-in-aid totaling $1,539,057 have been made to 225 investigators for the 1958-59 fiscal year. These grants brought to 408 the number of research awards made by the Association this year. Previously announced were 183 fellowship awards in the amount of $1,523,147.

The combined total of $3,062,204 is the largest sum to be awarded in a single fiscal year thus far under the Association's national research support program. Last year $2,341,115 was awarded nationally, while the Association's affiliates and chapters appropriated approximately $3,826,000 to support studies by investigators in their own geographic areas. The total channeled into research since the AHA became a national voluntary health agency 10 years ago now stands at approximately $31,500,000.

A complete list of grants-in-aid appears at the end of this section.

AHA SCIENTIFIC SESSIONS WILL PRESENT 120 PAPERS

A total of 120 original scientific papers, selected from over 360 submitted, will be presented at the American Heart Association's 31st Annual Scientific Sessions in San Francisco's Civic Center, Friday, October 24 through Sunday, October 26. In addition, there will be approximately 30 papers read by invited speakers.

Additional interest in the varied program to be presented this year will be provided with an all-day Scientific Session for Clinicians and joint participation in the Scientific Sessions by the American Society for the Study of Arteriosclerosis and the Microcirculatory Conference.

AHA GRANT-IN-AID APPLICATIONS DUE BY NOVEMBER 1

Applications for Heart Association grants-in-aid during the fiscal year beginning July 1, 1959 must be received by the Assistant Medical Director for Research at the AHA National Office, 44 East 23rd Street, New York 10, N. Y., not later than November 1, 1958. The deadline for submitting applications for Research Fellowships and Established Investigatorships was September 15.

All applications must be made on forms available from the AHA. Grants are made to non-profit institutions in direct support of a particular investigator, for a specific program of research under his direction. Grants are awarded in support of research in the cardiovascular field or basic sciences for periods of one to five years.

The Session for Clinicians, scheduled for Friday, October 24, under sponsorship of the Council on Clinical Cardiology, will include symposia on "Congenital Heart Disease," "Treatment of Intravascular Clotting," and "Peripheral Arterial Insufficiency." The clinicians will also discuss such subjects as "Clinical Evaluation of Chlorothiazide," "Traumatic Heart Disease," and "The 'Tough Case' of Bacterial Endocarditis." A panel discussion, "What's New in Arrhythmias," will be held. These sessions have been classified by the American Academy of General Practice as acceptable for credit for Academy members.

Following is a schedule of other highlights of the three-day Scientific Sessions:

Friday, October 24

Morning: Joint ASSA-AHA session on genetics; Scientific Sessions under sponsor

sh[illegible] of the Heart Association's Councils on Ci[illegible]ulation and Cardiovascular Surgery.

Afternoon: Scientific Session sponsored by th[illegible] Council on Rheumatic Fever and Con[illegible]ital Heart Disease; Joint Session of the A[illegible]ciation's Council on Circulation and the Mi[illegible]rocirculatory Conference, with symposia on "Vascular Thrombosis," "Cerebral Circulation," and "Vascular Reactivity."

Evening: Session on "Instrumental Study of the Heart and Circulation."

Saturday, October 25

Morning: General session on Applied Cardiovascular Research; Lewis A. Conner Memorial Lecture by John H. Gibbon, Jr., M.D., Professor of Surgery, Jefferson Medical College, Philadelphia, "on Maintenance of Cardio-Respiratory Functions by Extracorporeal Circulation"; George E. Brown Memorial Lecture by Lewis Thomas, M.D., Professor and Chairman, Department of Medicine, New York University College of Medicine, on the "Role of Hypersensitivity in Cardiovascular Disease"; and several papers of general clinical interest.

Afternoon: Panels on Arteriosclerosis to be presented jointly with the American Society for the Study of Arteriosclerosis.

Sunday, October 26

Morning: Simultaneous Scientific Sessions to be conducted by the Councils on Clinical Cardiology, High Blood Pressure Research, and Basic Science.

Afternoon: A special program designed to interest laymen as well as physicians, "Rewards of Research," arranged by the Council on Community Service and Education, followed by a session on Rheumatic Fever Secondary Prevention Programs, sponsored jointly by the Councils on Rheumatic Fever and Congenital Heart Disease and Community Service and Education, which will cover areas of general interest concerning the scientific basis of prophylaxis, the practical problems of applying this scientific knowledge, and areas still to be explored for further knowledge on this subject.

Evening: American Heart Association's Annual Dinner at the Fairmont Hotel.

A medical film program will be shown each day concurrent with the Scientific Sessions. As in previous years, a section of scientific and industrial exhibits will be on view.

Urge Early Registration

Registration and hotel accommodations forms are now available from the Association. As an inducement to early registration all physicians who register prior to the Scientific Sessions will receive an advance complimentary copy of the program booklet containing abstracts of the proceedings. These will be sold for $1.00 at the meeting.

AHA Assembly Meeting

The AHA Assembly will review national policies and activities of the Association at its Annual Meeting, Monday, October 27 and Tuesday, October 28 at the Hotel Fairmont.

Six Assembly Panels will be in session on Monday to discuss the following subjects: Research; Fund Raising and Public Relations; Relationships and Responsibilities Between National, State and Local Heart Associations; Community Service-Screening and Case Finding Programs; The Physician's Continuous Self-Education; and Membership.

On Tuesday morning, the general session of the Assembly will review Panel recommendations and elect officers and Board members of the Association.

AMERICAN MEDICAL ASSOCIATION ENDORSES POLICIES OF AHA

The House of Delegates of the American Medical Association recently adopted resolutions which expressed the medical profession's confidence in the programs of research, education and fund raising conducted by the American Heart Association and other major voluntary health agencies.

Meeting at the time of the AMA's annual convention in San Francisco, June 26, the House of Delegates adopted by a standing vote the following resolutions:

> "1.—That the House of Delegates reiterate its commendation and approval of the principal Voluntary Health Agencies.
>
> 2.—That it is the firm belief of the American Medical Association that these Agencies

should be free to conduct their own programs of research, public and professional education and fund raising in their particular spheres of interest.

3.—That the House of Delegates respectfully requests that the American Medical Research Foundation take no action which would endanger the constructive activities of the National Voluntary Health Agencies.

4.—That the Board of Trustees continue actively its studies of these perplexing problems looking forward to their ultimate solution."

The third resolution refers to efforts by United Funds to disburse, through the AMA's American Medical Research Foundation, money raised for "heart disease" and other causes. Despite the refusal of Heart Associations and other health agencies to join in federated fund raising plans, United Funds have included such causes in their appeals, thus receiving funds which in many cases remain unspent.

PROGRAM IS OUTLINED FOR JOINT ASSA-AHA SESSIONS

A program which includes a symposium on "Genetic Factors in Cardiovascular Disease," and Panels on the subject of arteriosclerosis will be presented jointly by the American Society for the Study of Arteriosclerosis and the American Heart Association at the AHA Scientific Sessions in San Francisco, October 24-26. This year for the first time the American Society for the Study of Arteriosclerosis is holding its Annual Meeting to coincide with the American Heart Association's Scientific Sessions.

Following is a tentative schedule of the joint ASSA-AHA program:

Friday, October 24, 9:00 a.m. to 12:30 p.m.

Symposium, "Genetic Factors in Cardiovascular Disease," Dr. Victor A. McKusick, Baltimore, and Dr. David Adlersberg, New York, Chairmen. This will include sessions on the following subjects: "Hypertension," participants: Sir George Pickering, Oxford, England, Dr. Caroline B. Thomas, Baltimore and Dr. Douglas R. Drury, Los Angeles; "Atherosclerosis," with Dr. Arthur G. Steinberg, Cleveland, Dr. Frederick H. Epstein, Ann Arbor, Mich. and Dr. Richard H. Osborne, New York; "Rheumatic Fever," with Dr. May G. Wilson, New York and Dr. Paul A. Lembcke, Los Angeles; and "Congenital Malformations," with Dr. Catherine A. Neill, Baltimore and Dr. McKusick. Discussion will be opened by Dr. Antonio Ciocco, Pittsburgh.

Saturday, October 25, 2:00 to 5:00 p.m.

Panels, "Emotional Factors in Atherosclerosis," Dr. Louis N. Katz, Chicago, Moderator; "Hypertension and Atherosclerosis," Dr. A. C. Corcoran, Cleveland, Moderator.

NEW CV RESEARCH INSTITUTE IN SAN FRANCISCO TO PRESENT SPECIAL SCIENTIFIC PROGRAM

The University of California Medical School in San Francisco will present a special scientific program on October 23 to mark the opening of its new Cardiovascular Research Institute. The date was chosen to permit attendance by physicians who will be in San Francisco for AHA's 31st Annual Scientific Sessions, October 24-26.

Speakers on the program include Sir George Pickering, Regius Professor of Medicine, University of Oxford, England; Dr. I. Lyon Chaikoff, Professor of Physiology, University of California, Berkeley; Dr. Malcolm McIlroy, First Assistant, Institute of Cardiology, London; and Dr. Julius H. Comroe, Jr., Director of the new Cardiovascular Research Institute.

Tickets for the special scientific program are obtainable from the University of California Medical Center, San Francisco 22, Calif.

MEETINGS CALENDAR

October 6-10: American College of Surgeons, Chicago. Michael L. Mason, 40 E. Erie Street, Chicago 11, Ill.

October 13-15: Association of American Medical Colleges, Swampscott, Mass. Mrs. Lotus R. Barnes, 2530 Ridge Ave., Evanston, Ill.

October 20-23: American Academy of Pediatrics, Chicago. E. H. Christopherson, 1801 Hinman Avenue, Evanston, Ill.

October 24-28: American Heart Association Annual Meeting and Scientific Sessions, San Francisco. American Heart Association, 44 East 23rd Street, New York 10, N. Y.

October 27-31: American Public Health Association, St. Louis, Mo. Berwyn F. Mattison, 1790 Broadway, New York 19, N. Y.

October 31-Nov. 1: Central Society for Clinical Research, Chicago. A. S. Weisburger, 2065 Adelbert Road, Cleveland 6, Ohio

November 6-8: Gerontological Society, Inc., 11th Annual Scientific Meeting. Philadelphia, Pa. Joseph T. Freeman, 1530 Locust Street, Philadelphia 2, Pa.

November 14-15: First annual Symposium of Cinefluorography, Strong Memorial Hospital, Rochester, N. Y. George H. Ramsey, Department of Radiology, Strong Memorial Hospital, Rochester 20, N. Y.

ABROAD

September 14-21: Third World Congress of Cardiology, Brussels. F. Van Dooren, 80 Rue Mercelis, Brussels, Belgium.

September 22-28: 16th International Congress of History of Medicine, Montpellier, France. Louis Dulieu, Montpellier, (Herault) France.

September 24-28: Third International Congress of Angiology, San Remo, Italy. M. Comel, Clinica Dermatologica, Universita di Pisa, Italy.

November 30-December 3: Fourth Latin-American Congress of Angiology, Santiago, Chile. Juan Borzone Galvez, Cassila 10256, Santiago, Chile.

LIST OF GRANTS

Following is a complete list of recipients of grants-in-aid awarded by the American Heart Association for the 1958-59 fiscal year, together with the institutions at which the scientists are working and the subjects of their studies.

Continued Grant Awards

Acheson, George H., M.D., University of Cincinnati College of Medicine, Cincinnati, for pharmacological studies of cardiac glycosides and related compounds having saturated lactone rings.

Berenson, Gerald S., M.D., Louisiana State University School of Medicine, New Orleans, for the continuation of studies of effects of inflammation on connective tissue.

Boutner, Reinhard H., M.D., Ph.D., Des Moines Still College of Osteopathy and Surgery, Des Moines, for study on electro-biochemistry as the basis of cardiac therapy.

Boyle, Edwin, Jr., M.D., Medical College of South Caroline, Charleston, for the investigation of a chemical method for measuring heparinoids in biological fluids.

Breese, Burtis B., M.D., The University of Rochester School of Medicine and Dentistry, Rochester, N.Y., for studies of streptococcal infection in children and their relation to rheumatic fever. Supported in full by the Orange County, N. Y. Heart Association.

Cheldelin, Vernon H., Ph.D., Oregon State College, Corvallis, for the study of oxidative patterns and electron transport in heart muscle.

Conn, Hadley L., Jr., M.D., Hospital of the University of Pennsylvania, Philadelphia, for the study of blood flow and myocardial metabolism with the aid of radioisotope techniques.

Elkinton, J. Russell, M.D., University of Pennsylvania School of Medicine, Philadelphia, for studies on the supra-optico-hypophyseal system in the cat pertaining to volume and concentration regulation; an effort to provide at least a partial explanation of certain phenomena observed in markedly edematous patients with heart disease.

Foulkes, Ernest C., Ph.D., The May Institute for Medical Research of the Jewish Hospital Association, Cincinnati, for the control of intracellular electrolyte composition.

Franke, Ernst K., Dr. Ing., University of Cincinnati and Cincinnati General Hospital, Cincinnati, for the study of the peripheral circulation in health and disease by means of heat flow calorimetry.

Fregly, Melvin J., Ph.D., University of Florida College of Medicine, Gainesville, to study the sensitivity, specificity and mechanism of the spontaneous sodium chloride aversion of hypertensive rats.

Gazes, Peter C., M.D., Medical College of South Carolina, Charleston, for the investigation of the role of heart contractile force in cardiovascular therapy.

Gibbon, John H., Jr., M.D., The Jefferson Medical College of Philadelphia, for a surgical method for the revascularization of the myocardium.

Glenn, William W. L., M.D., Yale University School of Medicine, New Haven, for enzymatic dissolution of intravascular clots.

Good, Robert A., M.D., Ph.D., University of Minnesota Medical School, Minneapolis, to study the basic mechanisms involved in etiology and pathogenesis of rheumatic fever and related diseases.

Gottschalk, Carl W., M.D., The University of North Carolina School of Medicine, Chapel Hill, for the mammalian micropuncture study of some of the physical factors in kidney function.

Green, Harold D., M.D., Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, to study the mechanism of and significance of epinephrine dilation (epinephrine reversal) in skeletal muscle, mesenteric and splenic arterial vascular beds.

Gross, Robert E., M.D., The Children's Hospital, Boston, for studies relevant to surgical treatment of congenital heart disease.

Guyton, Arthur C., M.D., The University of Mississippi Medical Center, Jackson, to study the further development and utilization of continuous recording of cardiac output by the fick principle.

Hall, E. Raymond, Ph.D., The University of Kansas, Lawrence, to study cardiovascular disease in free-living mammals other than man, correlated with habits, habitat and heritage.

Hamilton, Tom. R., M.D., University of Kansas School of Medicine, Kansas City, Kan., and Children's Convalescent Center, Kansas City, Mo., for a community-type study of children in rheumatic and nonrheumatic families.

Harden, K. Albert, M.D., Howard University College of Medicine, Washington, D. C., to study the pulmonary and cardiac dynamics in chronic pulmonary disease.

Helm, Robert A., M.D., Cincinnati General Hospital, for the clinical study of a spatial electrocardiogram of thirteen leads designed to have approximately uniform electrical fields.

Helmsworth, James A., M.D., University of Cincinnati College of Medicine, for a new method to bypass the heart for intracardiac surgery without extracorporeal oxygenation.

Hoffman, Brian F., M.D., State University of New York, Downstate Medical Center, Brooklyn, N. Y., to study electrophysiology of cardiac muscle, emphasizing the effects of anodal current and injury current on the transmembrane potentials, conductivity, rhythmicity and excitability of single cardiac fibers.

Holland, William C., M.D., Vanderbilt University School of Medicine, Nashville, Tenn., to study the mechanism of action of antifibrillatory drugs.

Hubbard, John P., M.D., University of Pennsylvania School of Medicine, Philadelphia, for study of streptococcal infection in a school population with a view to the primary prevention of rheumatic fever.

Jeanloz, Roger W., Ph.D., Massachusetts General Hospital, Boston, to study the chemistry and biochemistry of heparins.

Kaplan, Nathan O., Ph.D., Brandeis University, Waltham, Mass., for the study of metabolic significance of nucleotides in cardiovascular tissues.

Katz, Yale J., M.D., Ph.D., University of Southern California School of Medicine, Los Angeles, to study the augmentation of kidney function by revascularization of the kidney. Supported in full by the Long Beach, Calif. Heart Association.

Kay, Jerome H., M.D., University of Southern California School of Medicine, Los Angeles, for mitral valve replacement for the treatment of mitral insufficiency.

Kerby, Grace P., M.D., Duke University School of Medicine, Durham, N. C., to study the metabolism of acid mucopolysaccharides of ground substance.

Keys, Ancel, Ph.D., University of Minnesota, Minneapolis, to study the frequency of ischemic heart disease, the cholesterol-lipoprotein system and the habitual diets of populations.

Krayer, Otto, M.D., Harvard University Medical School, Boston, for a comparative study of the chronotropic cardiac action of the Rauwolfia alkaloids and related substances.

Ler, Maurice, M.D., Hektoen Institute for Medical Research of the Cook County Hospital, Chicago, to study the histopathology of the conduction system in congenital heart disease.

Liebelt, Robert A., Ph.D., M.D., Baylor University College of Medicine, Houston, to study the effect of the adrenal gland on obesity in mice.

Little, J. Maxwell, Ph.D., Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C., for the study of the excretion of epinephrine, norepinephrine, and 5-hydroxyindoleacetic acid in essential hypertension and experimental hypertension resulting from partial carotid sinus clamping.

Lukas, Daniel S., M.D., Cornell University Medical College, New York, to study the quantitation of valvular insufficiency.

Lundberg, W. O., Ph.D., The Hormel Institute, Graduate School of the University of Minnesota, Austin, to study the fat metabolism in relation to atherogenesis.

Mallov, Samuel, Ph.D., The Research Foundation of State University of New York, Syracuse, for the study of the reactivity of isolated strips and of the contractile proteins of the smooth muscle of blood vessels of experimental hypertensive animals.

Maybury, Robert H., Ph.D., University of Redlands, Redlands, Calif., to study the physical chemistry of proteins in nonaqueous solvents, including anhydrous hydrogen fluoride and deuterium oxide. Supported in part by the Long Beach, Calif. Heart Association.

McKenna, Joseph M., Ph.D., Seton Hall University, South Orange, N. J., to study the mechanisms of protection against circulatory collapse in hemorrhage and trauma.

Meng, H. C., M.D., Ph.D., Vanderbilt University School of Medicine, Nashville, Tenn., for the production of lipemia clearing factor(s) and its role in lipid metabolism and atherogenesis.

Orbison, J. Lowell, M.D., The University of Rochester School of Medicine and Dentistry, Rochester, N. Y., to study the relationship of the kidney to membrane permeability and fluid and electrolyte distribution in experimental hypertensive cardiovascular disease.

Osborn, John J., M.D., Stanford University Hospitals, San Francisco, to study the diagnosis and surgical treatment of congenital and acquired heart disease; extracorporeal circulation, gasometric analyses of flows and shunts. Cardiorespiratory physiology in open-chest surgery.

Overman, Richard R., Ph.D., The University of Tennessee, Institute of Clinical Investigation, Memphis, to study mechanisms of ionic distribution in experimental cardiovascular disorders.

Owens, James C., M.D., University of Colorado Medical Center, Denver, for experimental chronic myocardial insufficiency produced by coronary artery embolization.

Perry, H. Mitchell, Jr., M.D., Washington University School of Medicine, St. Louis, to study the relation of trace metals to atherosclerosis.

Richmond, Jonas E., Ph.D., Harvard University Medical School, Boston, for the role of the prosthetic group of proteins in the biosynthesis and metabolism of conjugated proteins.

Rodbard, Simon, M.D., Ph.D., The University of Buffalo Chronic Disease Research Institute, Buffalo, N. Y., to study the dietary patterns in the development and regression of experimental arteriosclerosis.

Ronwin, Edward, Ph.D., University of Minnesota Medical School, Minneapolis, for the study of the enzymes involved in blood clotting and their mechanism of action.

Rose, John C., M.D., Georgetown University Hospital, Washington, D. C., for pulmonary vasomotor activity.

Rudolph, Abraham M., M.B.B.Ch., M.D., The Children's Medical Center, Boston, to study the pulmonary hypertension in congenital heart disease.

Sanadi, D. Rao, Ph.D., University of California School of Medicine, Berkeley, for the mechanism of a-ketoglutarate oxidation and coupled phosphorylation.

Schmidt, Carl F., M.D., University of Pennsylvania School of Medicine, Philadelphia, for the study of physiology and pharmacology of the coronary circulation, with special reference to the influence of mechanical and nervous factors.

Seaman, Arthur J., M.D., University of Oregon Medical School, Portland, for a controlled long-term study of continuous anticoagulant therapy in coronary artery disease.

Sellers, Alvin L., M.D., Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles, for metabolic studies on the isolated perfused mammalian kidney.

Shore, Bernard, Ph.D., Washington University School of Medicine, St. Louis, Mo., to study the chemistry of heparin-catalyzed lipoprotein transformations.

Siegel, Alan C., M.D., The Children's Memorial Hospital, Chicago, for studies on the incidence, diagnosis, treatment and nonsuppurative complications of group A streptococcal infections in a general pediatric population, with particular reference to the attack rate and prevention of rheumatic fever.

Siperstein, Marvin D., M.D., Ph.D., University of Texas Southwestern Medical School, Dallas, for studies on factors influencing the destruction of cholesterol.

Smith, Jay A., Ph.D., The Chicago Medical School, to study the effect of various metabolic blocking agents on changes in metabolic rate produced by digitalis.

Smith, Richard T., M.D., The University of Texas Southwestern Medical School, Dallas, for changes in mechanisms of resistance and immunity related to age, particularly in regard to group A streptococcal infection.

Sobel, Harry, Ph.D., University of Southern California School of Medicine, Los Angeles, for investigation of the cellular proteins of heart tissue. Supported in full by the Long Beach, Calif. Heart Association.

Surawicz, Borys, M.D., The University of Vermont College of Medicine, DeGoesbriand Memorial Hospital and the Mary Fletcher Hospital, Burlington, to study the effect of potassium and calcium imbalance on the electrical and mechanical properties of the mammalian heart.

Swan, Henry, M.D., University of Colorado School of Medicine, Denver, for physiological and technical studies relating to cardiovascular surgery.

Swan, Roy C., M.D., Cornell University Medical College, New York, N. Y., to study the cation transport across cell membranes of skeletal muscle.

Szent-Gyorgyi, Albert, M.D., Ph.D., Institute for Muscle Research, Woods Hole, Mass., to study the chemical macromolecular and histological structure of muscle and chemistry of contraction cycle; mechanochemical coupling.

Szent-Gyorgyi, Andrew G., M.D., Institute for Muscle Research, Woods Hole, Mass., for studies on the structure of the contractile proteins and chemistry of contraction.

Taylor, C. Bruce, M.D., Presbyterian-St. Luke's Hospital, Chicago, for the study of atherosclerosis and lipid metabolism in the rhesus monkey and comparative studies in man.

von Kaulla, Kurt N., M.D., University of Colorado School of Medicine, Denver, to study fibrinolytic enzymes.

Wang, S. C., M.D., Ph.D., Columbia University College of Physicians and Surgeons, New York, for the central nervous control of circulatory system.

Waters, Levin L., M.D., Yale University School of Medicine, New Haven, Conn., for the modification of the lesions of experimental atherosclerosis.

Weller, John M., M.D., University of Michigan Medical School, Ann Arbor, for the investigation of abnormalities of electrolyte metabolism and acid-base balance in hypertension.

Wood, Harrison F., M.D., Irvington House, Irvington-on-Hudson, New York, for epidemiological studies of methods for prevention of rheumatic fever and rheumatic heart disease. Supported in part by the Sullivan County, N. Y. Heart Association.

Yu, Paul N., M.D., The University of Rochester School of Medicine and Dentistry, Rochester, N. Y., to study the pharmacodynamics of the pulmonary circulation in man. Supported in part by the Wyoming County, N. Y. Heart Chapter.

Zucker, Marjorie B., Ph.D., Sloan-Kettering Institute for Cancer Research, New York, for studies on platelets and thrombosis.

Zweifach, Benjamin W., Ph.D., New York University College of Medicine, New York, to study the delineation of physical and chemical factors affecting blood flow and transcapillary exchange.

New Approved Grants

Aikawa, Jerry K., M.D., University of Colorado School of Medicine, Denver, for the study of immuno-physiology.

Aladjem, Frederick, Ph.D., University of Southern California School of Medicine, Los Angeles, for immunochemical studies on human plasma lipoproteins.

Ambrus, Julian L., M.D., Ph.D., University of Buffalo School of Medicine and Roswell Park Memorial Hospital, Buffalo, N. Y., for studies on the therapeutic application of fibrinolytic enzymes.

Barnes, Frederick W., Jr., M.D., Ph.D., Johns Hopkins Hospital, Baltimore, for the study of regenerative cellular response to induced depletion of cellular proteins.

Bauer, Franz K., M.D., University of Southern California School of Medicine, Los Angeles, for determination of cardiac output by a direct recording technique, using radioiodinated human serum albumin, in patients with myocardial infarctions.

Benesch, Reinhold, Ph.D., Marine Biological Laboratory, Woods Hole, Mass., to study the relationship between chemical structure and diuretic activity in organic mercurials.

Bing, Richard J., M.D., Washington University Medical Service and Veterans Administration Hospital, St. Louis, Mo., for the study of cardiac metabolism and contractile proteins of heart muscle.

Blakemore, William S., M.D., University of Pennsylvania School of Medicine, Philadelphia, for the evaluation of Freeze-dried homografts and synthetic cloth mesh materials used to replace human blood vessels.

Bloch, Edward H., M.D., Ph.D., Western Reserve University School of Medicine, Cleveland, to study the sequential biophysical analysis of the effect of antigen-antibody reactions on the microcirculation and blood vessel walls in vivo.

Blumgart, Herrman L., M.D., Harvard University Medical School at Beth Israel Hospital, Boston, to study the metabolic aspects of urinary tract infections.

Booker, Walter M., Ph.D., Howard University College of Medicine, Washington, D. C., for studies on the effect of some cardiac drugs during hypothermia: Influence of cortisone on heart action.

Bottcher, Elizabeth J., M.D., Rochester General Hospital, Rochester, N. Y., to study elastic tissue as an autoantigen.

Boucot, Nancy G., M.D., Harvard University Medical School, Boston, for alterations in metabolism in renal disease.

Bozian, Richard C., M.D., New York University Post-Graduate Medical School, New York, for a genetic and metabolic study of familial hyperlipemia.

Brady, Allan J., Ph.D., University of California Medical Center, Los Angeles, for the study of myocardial tension related to transmembrane potentials and ion fluxes.

Brewster, William R., Jr., M.D., Massachusetts General Hospital, Boston, to study the mechanism of action of epinephrine, norepinephrine, the thyroid hormones and adrenal cortical steroids in effecting transfer and utilization of energy for contraction and relaxation of heart muscle.

Buckley, Nancy M., M.D., Albert Einstein College of Medicine of Yeshiva University, New York, for the study of cardiodynamics in valve disorders.

Case, Robert B., M.D., St. Luke's Hospital, New York, for detection of circulatory shunts by use of a radioactive gas.

Cogan, David G., M.D., Massachusetts Eye and Ear Infirmary, Boston, to study the aging processes as reflected in the cornea, specifically the relation of fat deposition in the cornea to atheroma in the blood vessels.

Connor, William E., M.D., State University of Iowa College of Medicine, Iowa City, to study the effect of estrogens upon blood coagulation in men and women: Its possible relationship to

atherosclerosis; also lipid metabolism and blood coagulation in atherosclerosis.

Conrad, Loyal L., M.D., Veterans Administration Hospital, Oklahoma City, to study the activation of the free wall of the right ventricle in the presence of right ventricular hypertrophy and right bundle branch block.

Crowell, Jack W., Ph.D., University of Mississippi Medical Center, Jackson, to study the effect of miliary embolism on circulatory dynamics.

Cugell, David W., M.D., Cook County Chest Hospital and Northwestern University Medical School, Chicago, to study the factors responsible for the development of cor pulmonale in chronic obstructive emphysema.

Cunningham, A. W. B., M.B., Ch.B., University of Texas Medical Branch, Galveston, to study the chemical exchanges in heart tissue culture.

Dallam, R. Duncan, Ph.D., University of Louisville School of Medicine, Louisville, Ky., to study thyroxine and oxidative phosphorylation.

Dennis, Clarence, M.D., Ph.D., State University of New York, Downstate Medical Center at Kings County Hospital, Brooklyn, N. Y., for the use of the heart-lung machine in cases of myocardial infarction in intractable shock.

Derrick, John R., M.D., University of Texas Medical Branch, Galveston, to formulate the symptom complex, pathology, and treatment of mesenteric artery insufficiency.

DeWall, Richard A., M.D., University of Minnesota Medical School, Minneapolis, to study perfusion techniques for reparative open intracardiac surgery.

Dexter, Lewis, M.D., Peter Bent Brigham Hospital, Boston, for the study of clinical and physiological correlations in valvular regurgitation.

Dingman, Joseph F., M.D., Tulane University School of Medicine, for study of hypothalamic-endocrine function in hypertension. Supported in full by the Louisiana Heart Association.

Drell, William, Ph.D., Veterans Administration Center, Los Angeles, for studies on the nature of the immediate precursors of sympathin.

Drury, Douglas R., M.D., University of Southern California School of Medicine, Los Angeles, for observations and experimental studies on rabbits with inherited hypertension.

Edelman, Isidore S., M.D., University of California Medical Center, San Francisco, to study relationships among serum pH, serum K^+ concentration and total exchangeable potassium and their influences on cardiac dynamics.

Edlestrom, H. E., Ph.D., University of North Dakota School of Medicine, Grand Forks, for a comparative study of the reactivity of blood vessels.

Eiber, Harold B., M.D., New York Medical College, New York, for studies on the physiological action of heparin.

Elkinton, J. Russell, M.D., University of Pennsylvania School of Medicine, Philadelphia, for clinical physiological and biochemical studies of renal failure.

Epstein, Franklin H., M.D., Yale University School of Medicine, New Haven, for the study of factors influencing renal concentrating ability.

Fawaz, George, Ph.D., M.D., American University of Beirut School of Medicine, Beirut, Lebanon, to study the effect of arrhythmias on the performance and metabolism of the isolated mammalian heart (Heart-Lung Preparation).

Finnerty, Frank A., Jr., M.D., District of Columbia General Hospital, Washington, D. C., to study the pathogenesis of postpartum hypertension.

Fishman, Alfred P., M.D., Columbia University College of Physicians and Surgeons and Presbyterian Hospital, New York, to study the interrelations between respiration and circulation in man.

Friedman, Meyer, M.D., Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital, San Francisco, for further studies concerning the metabolism of cholesterol.

Giebisch, Gerhard H., M.D., Cornell University Medical College, New York, for the study of ion transport across renal tubules of the amphibian and mammalian kidney utilizing micropuncture and microelectrode techniques.

Gilbert, Robert P., M.D., Northwestern University Medical School, Evanston, Ill., for the study of hemodynamics of endotoxin shock with special reference to its pathogenesis in monkeys and in man.

Goetz, Robert H., M.D., Albert Einstein College of Medicine of Yeshiva University, New York, for hemodynamic studies of the pulmonary circulation.

Green, Jack P., Ph.D., M.D., Yale University School of Medicine, New Haven, for the study of mechanism of action of dicoumarol and vitamin K_1.

Grisolia, Santiago, M.D., University of Kansas Medical Center, Kansas City, for the study of metabolism of phosphoglycerate.

Hanna, Calvin, Ph.D., University of Vermont College of Medicine, Burlington, for studies on tachyphylaxis.

Harrison, Tinsley, R., M.D., Medical College of Alabama, Birmingham, for the study of velocity and acceleration pressure pulses and correlation with other hemodynamic data in the human subject.

Hegnauer, A. H., Ph.D., Boston University School of Medicine, Boston, for in vitro studies of cardiac pathophysiology in experimental hypother-

mia, with special reference to susceptibility to ventricular fibrillation.

Hegsted, D. Mark, Ph.D., Harvard University School of Public Health, Boston, to study the role of magnesium in atherosclerosis.

Helpern, Milton, M.D., Office of Chief Medical Examiner, City of New York, for the study of pathologic findings in cases of sudden and unexpected death from occlusive coronary artery disease. Correlation of findings with circumstances.

Hertzler, Emanuel C., Ph.D., Kent State University, Kent, Ohio, for the study of serotonin, blocking agents and transmission in sympathetic ganglia. Supported in full by the Akron, Ohio District Heart Association.

Heymann, Walter, M.D., Western Reserve University School of Medicine, Cleveland, for the regulation of blood lipid concentration with special reference to pathogenesis of nephrotic hyperlipemia.

Hickam, John B., M.D., Indiana University Medical Center, Indianapolis, to study the effect of congestive heart failure on pulmonary function in patients with lung disease.

Hill, Robert M., Ph.D., University of Colorado School of Medicine, Denver, for myocardial chromoproteins and their derivatives as indicators of myocardial infaretion.

Hilton, James G., M.D., St. Luke's Hospital, New York, for the study of adrenal gland physiology.

Hoff, Hebbel E., Ph.D., M.D., and *Huggins, Russell A., Ph.D.*, Baylor University College of Medicine, Houston, Tex., for the dynamic and electrical analysis of the electrocardiographic changes produced by potassium intoxication.

Hollander, Walter, Jr., M.D., University of North Carolina School of Medicine, Chapel Hill, for studies on the action of antidiuretic hormone.

Holman, Ralph T., Ph.D., University of Minnesota Medical School, Minneapolis, for the study of polyunsaturated acids and the transport of lipides.

Holt, Joseph P., M.D., Ph.D., University of Louisville, Institute for Medical Research, Louisville, Ky., for studies on residual volume of the dog's ventricle.

Johnston, Frank R., M.D., Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C., to study experimental pulmonary hypertension.

Joos, Howard A., M.D., Childrens' Hospital Society of Los Angeles, for studies of vascular physiology in infancy and childhood.

Judson, Walter E., M.D., Indiana University Medical Center, Indianapolis, to study the relationship between cardiovascular and renal responses in patients with hyperkinetic circulatory states.

Karnovsky, Manfred L., Ph.D., Harvard University Medical School, Boston, for studies of polyene fatty acids in the adrenal gland, plasma lipoproteins and nervous tissue.

Katz, Louis N., M.D., Medical Research Institute, Michael Reese Hospital, Chicago, to study the metabolic and hemodynamic interrelationships in the intact myocardium.

Kelsey, F. E., Ph.D., University of South Dakota School of Medicine, Vermillion, to study the mechanism of action of digitoxin and related substances.

Keys, Ancel, Ph.D., University of Minnesota, Minneapolis, for the study of the effect of diet on blood serum cholesterol and lipoproteins in man.

Kuhns, William J., M.D., University of Pittsburgh School of Medicine, for the immunochemical studies of human diphtheria antitoxins—investigation of toxin-antitoxin complexes.

Kuo, Peter T., M.D., University of Pennsylvania School of Medicine, Philadelphia, for an investigation of vascular fluid dynamics and their influence upon intravascular distribution of plasma lipids and atherosclerosis.

Landowne, Milton, M.D., Levindale Hebrew Home and Infirmary, Baltimore, for studies in the pathophysiology of aortic and peripheral vascular disorders.

Lathem, Willoughby, M.D., University of Pittsburgh School of Medicine, for studies of renal hemoglobin transport.

Lazzarini, Abel A., Jr., M.D., New York University Post-Graduate Medical School, for studies of the metabolic and immunological changes occurring in transplanted tissues.

Leaf, Alexander, M.D., Massachusetts General Hospital, Boston, for the study of renal acidifying mechanisms.

Lewis, David H., M.D., Philadelphia General Hospital, Philadelphia, for the application of underwater acoustics to the diagnosis of heart disease.

Lewis, F. John, M.D., Ph.D., Northwestern University Medical School, Chicago, for a new membrane oxygenator for cardiopulmonary bypass.

Liebow, Averill A., M.D., Yale University School of Medicine, New Haven, Conn., for quantitative comparative studies of experimentally induced collateral circulation to the heart.

Lotspeich, William D., M.D., University of Cincinnati College of Medicine, Cincinnati, Ohio, to study the relation between kidney metabolism and several of its excretory functions.

Luchsinger, Peter C., M.D., District of Columbia General Hospital, Washington, D. C., to study the effect of O_2 breathing upon arterial and mixed venous blood gas composition and the hemodynamics of the pulmonary and systemic circulation in the cardiac patient.

MacDonald, Richard A., M.D., Mallory Institute

f Pathology, Boston City Hospital, to study e role of serotonin in cardiovascular and renal isease.

M hews, Martin B., Ph.D., LaRabida-University f Chicago Institute, University of Chicago, for e macromolecular structure and interactions of nnective tissue ground substance.

M ubbin, James W., M.D., Cleveland Clinic, leveland, Ohio, to study neural mechanisms in xperimental renal hypertension.

M ill, Henry C., Jr., M.D., Louisiana State Uniersity School of Medicine, New Orleans, to tudy electron microscopy of vascular lesions.

McIntosh, Henry D., M.D., Duke University School of Medicine, Durham, N. C., to study the reversibility of increased pulmonary vascular resistance.

McKusick, Victor A., M.D., Johns Hopkins Hospital, Baltimore, for a follow-up and extension of the family studies of Raymond Pearl.

Mehl, John W., Ph.D., University of Southern California School of Medicine, Los Angeles, for nutritional and metabolic studies on essential fatty acids.

Meiklejohn, Gordon, M.D., University of Colorado School of Medicine, Denver, for the study of fibrinolytic enzymes.

Meilman, Edward, M.D., Long Island Jewish Hospital, New Hyde Park, N. Y., to study isolation and properties of structural proteins in smooth muscle.

Mendlowitz, Milton, M.D., Mount Sinai Hospital, New York, to study the digital circulation in hypertension.

Mills, Lewis C., M.D., Hahnemann Medical College and Hospital, Philadelphia, to study the renal action of digoxin: effects on steroid and electrolyte excretion.

Moe, Gordon K., M.D., Ph.D., State University of New York Upstate Medical Center, Syracuse, to study the nature of atrial fibrillation.

Mommaerts, Wilfried F. H. M., Ph.D., University of California Medical Center, Los Angeles, to study the biophysical aspects of cardiac activity. Supported in full by the Long Beach, Calif. Heart Association.

Montgomery, A. Vernon, Jr., M.D., Ph.D., University of Colorado School of Medicine, Denver, to study genesis and control of ventricular fibrillation.

Morehouse, Margaret G., Ph.D., University of Southern California School of Medicine, Los Angeles, for the distribution, synthesis and utilization of heart lipids under normal and pathological conditions. Supported in full by the Long Beach, Calif. Heart Association.

Mulder, Peter V., M.D., University of Chicago School of Medicine, for chemical and physiological studies on the transplanted canine heart.

Nelson, Russell M., M.D., Ph.D., University of Utah College of Medicine, Salt Lake City, to study a method for the determination of blood loss during surgical procedures, employing "washed field" techniques.

Nyboer, Jan, M.D., Harper Hospital, Detroit, for the adaptation of an aperiodic frictionless suspension for study of cardio-respiratory ballistics.

Olson, Robert E., Ph.D., M.D., University of Pittsburgh Graduate School of Public Health, to study the effect of congestive heart failure due to valvular disease upon the contractile proteins in dogs and man.

Padawer, Jacques, Ph.D., Albert Einstein College of Medicine of Yeshiva University, New York, to study physiology and biochemistry of the mast cell in relation to cardiovascular function and disease.

Park, Charles R., M.D., Vanderbilt University School of Medicine, Nashville, Tenn., to study the relationship of growth hormone to carbohydrate metabolism and glucose transport in the isolated heart.

Paul, Oglesby, M.D., Presbyterian-St. Luke's Hospital, Chicago, for a longitudinal study of coronary heart disease.

Phillips, Gerald B., M.D., Columbia University College of Physicians and Surgeons, New York, for studies on the individual phospholipids of human serum.

Pilgeram, Laurence O., Ph.D., St. Barnabas Hospital, University of Minnesota Medical School, Minneapolis, for studies on the biochemistry of arteriosclerosis.

Pipberger, Hubert V., M.D., Georgetown University Medical Center, Washington, D. C., for the study of orthogonal vectorcardiography and electrocardiography.

Pontius, Robert G., M.D., Children's Hospital of Pittsburgh, to study cardiac metabolism in humans related to extracorporeal circulation.

Porter, John W., Ph.D., University of Wisconsin and Veterans Administration Hospital, Madison, to study the mechanism of enzymatic synthesis of fatty acids.

Pritchard, Jack A., M.D., University of Texas Southwestern Medical School, Dallas, for acquired alterations of the hemostatic mechanism during pregnancy.

Rapaport, Elliot, M.D., Mount Zion Hospital, San Francisco, for the applicability of an intracardiac thermistor probe in the measurement of cardiac output and the detection of left to right intracardiac shunts.

Rhinesmith, Herbert S., Ph.D., Allegheny College, Meadville, Pa., to study the chains in normal adult human hemoglobin; separation and amino acid sequence.

Rogers, Lloyd S., M.D., State University of New York Upstate Medical Center, Syracuse, for electropolarographic studies of myocardial oxygenation. I. Evaluation of the effect of the Beck I operation on myocardial oxygenation following coronary occlusion in the dog.

Rosenman, Ray H., M.D., Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital, San Francisco, for a study of the mechanism of hypercholesteremia and hyperlipemia in experimental nephrosis in rats.

Rushmer, Robert F., M.D., University of Washington School of Medicine, Seattle, to study the distribution of blood flow in intact dogs.

Rutstein, David D., M.D., Harvard University Medical School, Boston, to study the factors affecting lipoid deposition in human aortic cells in tissue culture.

Salisbury, Peter F., M.D., Ph.D., Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles, for the study of pulmonary edema: factors which influence its development and regression in the anesthetized dog.

Saslaw, Milton S., M.D., National Children's Cardiac Hospital, Miami, Fla., to study the efficacy of medication with antibiotics in eliminating B hemolytic streptococcus from deep tissues.

Scher, Allen M., Ph.D., University of Washington School of Medicine, Seattle, to study body surface potentials produced by an intracardiac dipole.

Schmidt-Nielsen, Bodil, Ph.D., Duke University, Durham, N. C., to study the renal mechanism for urea and salt excretion.

Schwartz, William B., M.D., New England Center Hospital, Boston, to study the renal regulation of acid-base equilibrium.

Schweet, Richard S., Ph.D., City of Hope Medical Center, Duarte, Cal., for the study of intermediate stages in protein synthesis.

Shapiro, Alvin P., M.D., University of Pittsburgh School of Medicine, for studies of the relationship of hypertensive vascular disease and experimental chronic pyelonephritis.

Sharp, John T., M.D., University of Buffalo School of Medicine, Buffalo, N. Y., for a study of the mechanical properties of the lungs in pulmonary edema.

Sieker, Herbert O., M.D., Duke University School of Medicine and Veterans Administration Hospital, Durham, N. C., for a study of cardiopulmonary function in obesity.

Simonson, Ernst, M.D., University of Minnesota Medical School, Minneapolis, to study the central nervous system involvement in essential hypertension.

Singer, Thomas P., Ph.D., Edsel B. Ford Institute for Medical Research, Henry Ford Hospital, Detroit, Mich., to study electron transport mechanisms in heart and other tissues.

Sirak, Howard D., M.D., and *Starkey, Walter L., Ph.D.*, Ohio State University College of Medicine, Columbus, to study the development of prosthetic valves for the human heart.

Spencer, Merrill P., M.D., Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C., to study the direct measurement of blood flow in humans.

Stamler, Jeremiah, M.D., City of Chicago Board of Health, for a long-term clinical-epidemiologic investigation of a practicable dietary regimen for lowering serum cholesterol and for reducing risk of myocardial infarction in high-risk middle-aged males.

Stefanini, Mario, M.D., St. Elizabeth's Hospital, Boston, for development and evaluation of substances with direct and indirect fibrinolytic activity in vivo for the control of venous and arterial thromboembolism.

Stetson, Chandler A., Jr., M.D., New York University College of Medicine, to study the participation of the coagulation mechanism in immunologic events.

Swell, Leon, Ph.D., Veterans Administration Center, Martinsburg, W. Va., to study cholesterol metabolism: mechanism of absorption and regulation in the blood.

Takaro, Timothy, M.D., Veterans Administration Hospital, Oteen, N. C., to study the development of a vessel coupling device for the rapid anastomosis of blood vessels by mechanical means, using stainless steel sutures.

Taussig, Helen B., M.D., Harriet Lane Home, Johns Hopkins Hospital, Baltimore, to study the etiology of congenital malformations of the heart and great vessels.

Taylor, Henry L., Ph.D., University of Minnesota School of Public Health, Minneapolis, to study death rates and physical activity among railroad workers with special reference to coronary heart disease in middle aged men.

Tobian, Louis, Jr., M.D., University of Minnesota Medical School, Minneapolis, for studies on the physiology of hypertension and the renal antihypertensive mechanism in man and experimental animals.

Umberger, Charles J., Ph.D., Office of Chief Medical Examiner, City of New York, for study of the composition of the lipid fraction removed from the coronary arteries in acute heart disease.

Von Korff, Richard W., Ph.D., University of Minnesota Medical School, Minneapolis, for investigations on the chemical nature of fibrinogen, fibrin and fibrinopeptide.

Walker, Sheppard M., Ph.D., University of Louisville School of Medicine, Louisville, to study the effect of electric current and certain metabolites on cardiac automaticity.

Warner, Homer R., M.D., Ph.D., University of Utah College of Medicine and Latter-Day Saints Hospital, Salt Lake City, to study the influence of changes in peripheral resistance and posture on backflow in the aorta of patients with aortic insufficiency.

Warren, James V., M.D., Duke University School of Medicine, Durham, N. C., to study the determinants of cardiac output in man.

Wasolowski, Sigmund A., M.D., State University of New York Downstate Medical Center and Kings County Hospital, Brooklyn, for the development and application of a test to determine the blood flow to a given local part.

Wessler, Stanford, M.D., Harvard University Medical School at Beth Israel Hospital, Boston, for studies in intravascular thrombosis.

Wilde, Walter S., Ph.D., University of Michigan Medical School, Ann Arbor, for localization of nephron transport by stop flow analysis.

Wilhelmj, C. M., M.D., Creighton University School of Medicine, Omaha, to study nerohormonal factors in hypertension.

Wilson, Hugh E., M.D., University of Texas Southwestern Medical School, Dallas, to study the gradual closure of septal defects.

Wilson, John L., M.D., American University of Beirut School of Medicine, Beirut, Lebanon, for the study of the rheumatic and congenital heart diseases in the Middle East.

Witt, Peter N., M.D., Research Foundation of State University of New York, Syracuse, for an investigation of the mechanism of action of drugs with positive inotropic effect on the heart with particular regard to their effect on ion movements.

Wong, Harry Y. C., Ph.D., Howard University College of Medicine, Washington, D. C., to study the role of exercise and endocrine glands in the alteration of blood cholesterol, phospholipids and lipoproteins in relation to atherosclerosis. Supported by the Hawaii Heart Association.

Wood, John C., M.D., Hospital of the University of Pennsylvania, Philadelphia, to study hormone effects on electrolyte distribution, electrolyte transfer kineties and other metabolic parameters in the isolated dog heart.

Zilversmit, D. B., Ph.D., University of Tennessee School of Medicine, Memphis, to study the relation of hypertension to experimental atherogenesis.

Note: Since publication of the list of AHA Fellowships in the April, 1958 issue of CIRCULATION, the Kansas Heart Association has provided funds to support the Research Fellowship of Miriam A. Derks, University of Kansas Medical Center.

In addition, the Colorado Heart Association has provided $5,000 for the National Research Support Program not assigned to a specific person or project.

AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

PROGRAM AND PROCEEDINGS OF THE TWELFTH ANNUAL MEETING AT THE WHITCOMB HOTEL AND THE CIVIC AUDITORIUM, SAN FRANCISCO, CALIFORNIA, OCTOBER 24, 25, AND 26, 1958

In Conjunction with the American Heart Association

(All papers except the Addresses will be limited to 10 minutes for presentation plus 5 minutes for discussion.)

FRIDAY MORNING

OCTOBER 24, 1958

8:00 a.m.-5:00 p.m. Registration. Mezzanine, Hotel Whitcomb.

9:00 a.m.-12:00 noon. Civic Auditorium

Genetic Factors in Cardiovascular Disease. Joint Symposium with the A.H.A.

FRIDAY AFTERNOON

CRYSTAL BALLROOM, WHITCOMB HOTEL

Forrest E. Kendall, Presiding

2:00

1. Is Increased Filtration Distance in the Arterial Wall a Factor in Atherogenesis?

C. Bruce Taylor, Arlene McGuigan, LaVerne Cox and G. E. Cox. From the Departments of Pathology and Surgery, Presbyterian-St. Luke's Hospital, Chicago, Ill.

It has been suggested that lipids accumulate in scarred thickened arterial walls because lipoproteins, traversing an increased filtration distance, disintegrate and the lipids precipitate. For testing this concept, segments of thick arterial scars were produced by freezing 4 mm. segments of the aorta and the iliac arteries in rhesus monkeys having normal serum cholesterol levels. The animals were kept on a low-fat cholesterol-free diet for 6 to 13 additional weeks in order that arterial repair could be completed in a normocholesterolemic (mean 150 mg. per cent) plasma environment. These same animals were then made hypercholesterolemic (mean 397 mg. per cent) by placing them on an adequate diet containing 1.6 per cent cholesterol and 20 per cent butter fat. After several months of hypercholesterolemia, additional arterial segments were frozen and allowed to heal in this hypercholesterolemic environment. About 2 months later the animals were autopsied and the thickened aortic and iliac arterial scars studied microscopically. Twelve monkeys were used in the experiment, but because of the untimely death of some of the animals there were 45 arterial scars in 6 animals that were adequate for evaluation. All of 15 arterial scars that healed in a hypercholesterolemic environment accumulated lipids, as had been observed in previous studies (Circulation **10**: 613, 1954). Atherosclerosis also developed in uninjured aortic and major arterial segments and in the coronary arteries of these animals (also observed previously, Fed. Proc. **16**: 374, 1957). However, contrary to our expectations, the 30 scars that had been allowed to heal in a normocholesterolemic environment did not seem to show an increased propensity to accumulate lipids when subsequently exposed to a hypercholesterolemic environment. In 20 of the lesions we found no accumulated lipids. Ten of these lesions showed meager lipid accumulations that were primarily confined to either the surfaces or the margins of the arterial scars.

2:10 Discussion

2:15

2. Sclerotic Vascular Changes Following Reduction of Arterial Distensibility

mon Rodbard. From the University of Buffalo Clinic Disease Research Institute, Buffalo, N. Y.

Each layer of the arterial wall can be shown to have specific responses to the application of mechanical forces. Thus, endothelial cells are flattened at sites of increased pressure; with reduced pressure these cells round up and may proliferate.

Media responds to shock waves and to tension. Placement of stainless-steel wires in the aortas of fifty chicks was followed by fraying of the ends of contiguous elastic fibers; islets of the adjacent media became transformed into avascular hyalinized matrix, containing round clear encapsulated cells, and staining characteristically for cartilage. The islets were located on both sides of the wire along the radius of the vessel. The cartilaginoid islets were surrounded by perichondrial capsules. In older specimens calcium deposition in the matrix became evident. These findings suggest that the prevention of normal expansion of an arterial segment exposes the wall to recurrent hammer blows on the arrival of each pulse wave. Metamorphosis of the media results in the formation of chondroid, a shock-absorbing tissue.

The wall of the vessel on the cardiac side of the wire became thickened, while that peripherad became thinned, in accord with differences in pressure at these sites. In several specimens saccular aneurysms developed adjacent to the wire, where the wall had been weakened by medial injury.

These results support the concept that vascular structure is determined to a significant degree by the action of mechanical forces.

2:25 Discussion

2:30

3. Acid Mucopolysaccharide Content of The Aorta in Cholesterol-Fed Rabbits

Alfred Jay Bollet, Chuni Wang and David Adlersberg. From The Department of Medicine, Wayne State University College of Medicine, Detroit, Michigan and The Department of Medicine, Mount Sinai Hospital, New York, N. Y.

Histochemical techniques have suggested an increase of acid mucopolysaccharide in the aorta of cholesterol-fed rabbits during the early phases of atherogenesis. This increase was less apparent after the development of severe atherosclerosis.

The acid mucopolysaccharide content of the aorta of rabbits that were fed daily 1 Gm. of cholesterol without an additional fat vehicle, was restudied, with the use of chemical methods of analysis. After periods of 1 to 7 months of feeding the aortas were removed, dried and defatted, extracted with 0.5 N NaOH, and the acid mucopolysaccharide isolated after removal of protein. The uronic-acid content of the mucopolysaccharide was determined by the carbazole and orcinol methods, before and after digestion with testicular hyaluronidase. Histochemical observations of the arteries and other tissues and serial serum lipid determinations were made on the same animals.

Total serum cholesterol levels rose gradually from 50 to 1476 mg./100 ml. after 3 months of cholesterol feeding, and levelled off at around 1,200 mg./100 ml. The elevations of serum phospholipids, triglycerides and total lipids fell behind those of serum cholesterol, as previously observed. Aortas of normal rabbits contained 341 ± 3.9 mg. uronic acid in mucopolysaccharide/100 Gm. dried fat-free tissue by the carbazole method; the carbazole/orcinol ratio was 1.5. After hyaluronidase incubation, the concentration averaged 175 ± 10.4 mg. per cent (carbazole). No changes in these levels were noted in rabbits fed cholesterol for 34, 62 and 100 days, despite progressive increase in serum lipids and development of 1 to 2 plus atherosclerosis; the corresponding concentrations of the aortas were 342, 312 and 341 mg. per cent (carbazole). Only in rabbits fed cholesterol for 186 days and more was there a decided increase in the mucopolysaccharide content of the aorta to an average of 512 ± 36 mg. per cent by the carbazole method ($p = > .01$). No change occurred in the carbazole/orcinol ratio (1.3) or in the amount of mucopolysaccharide after hyaluronidase digestion.

These observations indicate that an increase in the mucopolysaccharide concentration of the aorta occurs in the cholesterol-fed rabbit, but only after prolonged feeding with high serum lipid levels maintained over several months and with the development of moderate to severe atherosclerosis. Caution is advisable in the interpretation of histochemical findings concerning the connective tissue ground substance during atherogenesis.

2:40 Discussion

2:45

4. Further Observations on Ulcerated Arteriosclerotic Lesions of the Abdominal Aorta in Cockerels

Ruth Pick and Louis N. Katz, with the assistance of Mr. P. Johnson and Mrs. D. Century. From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

Decreasing the protein content of a high cholesterol-oil diet has been shown to enhance its atherogenicity. Estrogens, when added to such a diet, exerted their usual protective action on the coronary arteries. However, in the abdominal aorta, this combination led to ulcerated and hemorrhagic plaques in half of the birds, with the pathology extending into the media. Recently, a therapeutic type of estrogen experiment was

made with the low protein, high cholesterol-oil diet. All birds were on this diet for a period of 5 to 10 weeks; ten were killed at 5 and 10 weeks respectively, as controls. The severity of lesions increased with the duration of the diet, but no ulcerations or hemorrhages were seen. At the end of 5 weeks on this diet the birds were divided into 3 more groups of 10 each: 1, an estradiol benzoate (1 mg./bird/day, 5 days/week); 2, a premarin (25 mg./bird/day, 5 days/week); 3, another premarin (as (2) above plus 150 mg. on the sixth and seventh days). Estrogens led to regression of coronary atherosclerosis, and, in group 3, of the abdominal aortic lesions. In fact, complete healing occurred in the aorta in some of these birds. However, ulceration and hemorrhage in the abdominal lesions were seen in 2 of 4 birds of group 3 killed at the end of 2 weeks. These results, in connection with our previous data, suggest the possibility that ulceration and hemorrhage may be an early stage in regression, occurring before healing is accomplished. It remains to be determined whether this occurs only in the abdominal aorta or in other vascular beds as well.

2:55 Discussion

3:00

5. Diet-Induced Tendency toward Atherosclerosis in Cockerels Reduced by Exercise and Male Hormone

Harry Y. C. Wong, Frank B. Johnson, and Abbie K. Wong. From the Department of Physiology, Howard University College of Medicine, and Armed Forces Institute of Pathology, Washington, D. C.

Earlier studies in our laboratory showed that exercise and testosterone propionate either singly or in combination for a few weeks resulted in a marked reduction in the formation of aortic and coronary atherosclerosis in young cockerels and capons fed a high cholesterol and cottonseed oil diet. The present investigation was undertaken to determine the effects of exercise and testosterone propionate on a long-term study on the aorta and coronary arteries of cockerels fed an "atherogenic" diet of 1 per cent cholesterol and 5 per cent cottonseed oil mixed with plain chicken starter mash. Seven groups of cockerels were used in the experiment: 1, controls on plain mash without therapy; 2, controls on plain mash but exercised; 3, controls on plain mash treated with testosterone propionate; 4, cholesterol-fed only; 5, similarly treated as group 4 except that this group was exercised; 6, cholesterol-fed treated with testosterone propionate; 7, similarly treated as group 6 except these were exercised. Exercise consisted of running in a treadmill twice daily 5 days/week at 6 ± 1 rpm for 30 min., or approximately 700 yards daily. At the end of the 15th week, the following results were observed: 1. Cholesterol-fed cockerels not exercised had the highest incidence of aortic atherosclerosis and blood cholesterol. 2. Treating birds with testosterone propionate or exercised resulted in a lowering of the blood cholesterol and a marked reduction in severity of aortic atherosclerosis, compared to the cholesterol-fed-only group. 3. The combination of exercise and testosterone propionate further decreased the severity of aortic atherosclerosis and the blood cholesterol, compared to the cholesterol-only group. 4. The blood cholesterol of the control birds, fed on plain mash exercised or treated with testosterone propionate, was not different from that of those fed on plain mash. The influence of exercise and testosterone propionate on the coronary arteries will be presented.

3:10 Discussion

3:15

6. The Rate of Lipolysis of Saturated and Unsaturated Fats by Post-Heparin and Endogenous Plasma Lipoprotein Lipase

H. Engelberg. From the Cedars of Lebanon Hospital, Los Angeles, Calif.

Many studies have shown that the ingestion of unsaturated vegetable oils does not elevate the serum cholesterol and lipoproteins in most human beings, whereas a highly saturated animal fat intake usually results in hypercholesterolemia and hyperbeta-lipoproteinemia. Since much experimental evidence indicates that lipoprotein lipase normally functions in the removal of neutral fat from the bloodstream, the rate of in vitro lipolysis of saturated and unsaturated fat substrates by post-heparin and endogenous human plasma lipoprotein lipase was investigated.

The fat substrates used were emulsions of cream and cottonseed oil, and human low-density lipoproteins separated by ultracentrifugation after the ingestion of large quantities of cream and safflower oil. Unesterified fatty acids were measured at 0, 10, 20 and 30 minutes after incubation, at 37 C., with plasma aliquots. The data obtained in 12 experiments almost uniformly showed that the unsaturated fats were split at a faster rate than the saturated ones. The difference in the rate of lipolysis between unsaturated and saturated fats varied from 4:3 to 5:1. These results indicate that, although other metabolic dissimilarities undoubtedly exist at tissue and cellular levels, the contrast in the efficiency of lipolysis of the two types of fats by plasma lipoprotein lipase is an important factor, determining their different effects upon serum lipid levels.

3:2 **Discussion**

3:3

7 **Changes in Blood Coagulation During the Clearing of Lipid Emulsions in Vitro**

obert L. Hirsch, and Aaron Kellner. From The De artment of Pathology, The New York Hospital-Cornell Medical Center, New York, N. Y.

When plasma from rabbits or human beings, given heparin intravenously (7.5 mg./Kg. and 1.0 mg. Kg., respectively), was incubated in vitro with lipid emulsions, the clotting time of the mixture, previously prolonged, was reduced strikingly as clearing proceeded. The increased coagulability in general paralleled the rate and degree of clearing. In systems containing sodium citrate and buffered at pH 7.0 or below, there was a progressive and substantial reduction of the recalcification time, often to normal, as the optical density of the mixture decreased. When no citrate was added to the medium, the mixture of plasma and lipid emulsion usually clotted solidly during the course of clearing. No change in coagulability was noted when the plasma was incubated without lipid emulsion, when the clearing enzyme was inactivated by heat, or when heparin was added in vitro to a mixture of normal plasma and lipid emulsion. Protamine sulphate and toluidine blue titrations done before and after clearing revealed a sharp diminution in heparin activity.

These observations suggest that during the course of the clearing reaction in vitro heparin is either destroyed or its anticoagulant properties are inhibited, or that a mechanism for clot formation is initiated which cannot be blocked by heparin. The findings may serve to explain, in part at least, the increased coagulability of blood observed in human beings following the ingestion of a fat-rich meal.

3:40 **Discussion**

3:45

8. **The Relationship of Increased Clearing-Factor Response to Concentration of Serum Lipids and Hypoalbuminemia in Laennec's Cirrhosis**

Saul P. Baker, Harold Levine, Liebert Turner, and Alvin Dubin. From the Department of Medicine, The Chicago Medical School, and the Hektoen Institute for Medical Research of the Cook County Hospital, Chicago, Ill.

A standardized in vitro method for the evaluation of heparin-activated clearing-factor (lipoprotein lipase) response has previously been reported in the program of this Society (Circulation **14:** 49 1956). While studying the effect of age on this test, it was incidentally observed that patients with primary diagnoses of chronic alcoholism and/or Laennec's cirrhosis demonstrated a significantly increased clearing-factor response (Circulation **15:** 889, 1957). In view of the observation that there is a lesser incidence of atherosclerosis in patients diagnosed as having Laennec's cirrhosis, more extensive studies have been made on a larger group, comprising 67 patients to date, having various types of hepatic pathology or jaundice. Twenty-three of these subjects demonstrated clinical and laboratory evidence of Laennec's cirrhosis. Laboratory evaluations included those of total and ester cholesterol, serum bilirubin, icterus index, BSP, total proteins and A/G ratio, cephalin flocculation, thymol turbidity, gamma globulin turbidity, and alkaline phosphatase.

These studies have confirmed the presence of an increased clearing-factor response in Laennec's cirrhosis. Furthermore, there appears to be no correlation between clearing-factor response and levels of total serum lipids, or lipid phosphorus, these being within the normal range. Serum total cholesterol generally ranged below 200 mg./100 ml. Percentage of serum cholesterol esters was almost uniformly low, being below 50 per cent (below 75 mg./100 ml.). The serum cholesterol/lipid phosphorus ratio appears to be related to the clearing-factor response. Hypoalbuminemia produced no depressant effect upon clearing-factor response, the greatest response being observed with serum albumin below 3.0 Gm./100 ml.

Perfusion experiments in rats have demonstrated that the normal rat liver inactivates or attenuates clearing factor (Quart. J. Exper. Physiol. **39:** 261, 1954). It is therefore suggested that the increased clearing-factor response in patients with Laennec's cirrhosis is related to their parenchymal liver cell damage. A possible interrelationship may exist between clearing-factor response, cholesterol/lipid phosphorus ratio, lipid metabolism, and atherosclerosis in man.

3:55

9. **Removal of Lipoprotein Lipase from the Blood by the Normal and Diseased Liver**

William E. Connor and John W. Eckstein. From the Cardiovascular Research Laboratories, Department of Internal Medicine, State University of Iowa College of Medicine, Iowa City, Ia.

Hepatic vein catheterization was performed in 5 normal human beings, 5 human beings with portal cirrhosis, 10 normal dogs, and 3 dogs with hepatic necrosis. High blood levels of lipoprotein lipase (LPL) were induced by intravenous heparin. Post-heparin plasma samples were obtained simultaneously from the hepatic and femoral or antecubital veins and incubated 2 hours with a standard coconut oil emulsion. LPL activity was

measured by optical density change (△OD) and glycerol production after incubation.

LPL activity of all normal subjects was greater in peripheral than in hepatic vein blood. In 4 of the normal dogs additional samples obtained at laparotomy showed LPL activity to be almost identical in portal and femoral vein blood.

The △OD difference, i.e., antecubital-minus-hepatic venous blood, averaged 0.172 ± 0.038 units ($p < 0.001$) in normal human beings, and 0.043 ±0.033 ($p < 0.05$) in cirrhotic patients. Glycerol production difference across the liver averaged 0.39 ± 0.08 μM/ml. ($p < 0.001$) in normals and 0.06 ± 0.15 ($p > 0.2$) in cirrhotics. The healthy liver extracted significantly more LPL than the diseased liver ($p < 0.001$).

The △OD difference across the liver averaged 0.151 ± 0.067 units ($p < 0.001$) in normal dogs and 0.038 ± 0.010 ($p < 0.02$) in dogs with hepatic necrosis. Glycerol production difference averaged 0.22 ± 0.13 μM/ml. ($p < 0.001$) in normal, and 0.04 ± 0.01 ($p < 0.05$) in diseased dogs. Again the normal liver removed significantly more LPL ($p < 0.02$).

These observations in man and the dog show that the normal liver removes LPL from blood. Liver disease prevents the usual hepatic extraction of LPL.

4:05 Discussion

4:15

10. Study of Possible Role of Lipoprotein Lipase Deficiency in Experimental Nephrotic Hyperlipemia

Ray H. Rosenman and Sanford O. Byers, From the Mount Zion Hospital, Harold Brunn, Institute, San Francisco, Calif.

The following studies were made to evaluate any possible role of deficiency of heparin or lipoprotein lipase which might contribute causally to experimental nephrotic hyperlipemia in rats. 1. Nephrotic (rabbit anti-rat, kidney serum) and control rats were serially bled after I.V. heparin; comparable prolongation of blood-clotting time and requirement for protamine neutralization were found in both groups. 2. Urine collected from groups of nephrotic and control rats during I. V. heparin administration did not contain identifiable lipoprotein lipase and did not differ in ability to prolong blood-clotting time. 3. Nephrotic rats were found normally capable of releasing lipoprotein lipase following heparinization. Thus the ability of postheparin nephrotic plasma to clear lipemic turbidity and release glycerol in an activated coconut oil emulsion was comparable to that of control rats' post-heparin plasma. 4. Deficient "clearing" and glycerol release were observed when post-heparin plasma was added to a coconut oil nephrotic plasma substrate. This response was normalized by in vitro addition of albumin or when the nephrotic plasma was obtained from nephrotic rats infused with albumin just prior to bleeding. Thus the nephrotic rats' plasma normally supported triglyceride hydrolysis when albumin only was added. 5. The "clearing" of post-heparin nephrotic lipemic plasma was markedly augmented and completely normalized by addition of albumin in vitro or when the plasma was obtained from nephrotic rats infused with albumin just prior to bleeding.

The results fail to implicate any abnormal renal loss of endogenous heparin or lipoprotein lipase or any abnormality of lipase metabolism in the nephrotic rat, and they support our previous studies of the primary causal role of deficiency of circulating albumin in the hyperlipemia of the nephrotic rat.

4:25 Discussion

4:30-5:30 p.m. Business Session

SATURDAY MORNING
CRYSTAL BALLROOM,
WHITCOMB HOTEL

Howard A. Eder, Presiding

9:00

11. Synthesis of Low and High Density Lipoproteins by Rat Liver Slices

Charles Radding and Daniel Steinberg. From the Section on Metabolism, National Heart Institute, National Institutes of Health, Bethesda, Md.

The lipid-protein linkages of lipoproteins appear for the most part to be noncovalent. Nevertheless, the composition of the major classes of serum lipoproteins is rather closely defined. The nature of the processes leading to the synthesis and release of these lipid-protein conjugates and the mechanisms controlling their rate of formation might be studied to advantage in an in vitro system. Preliminary experiments with rat liver slices incubated in serum have demonstrated the incorporation of C^{14}-labeled amino acids into protein fractions with density less than 1.063 and with density between 1.063 and 1.21. These labeled proteins, presumably lipoproteins, were also released into the medium. In 3 successive 48 hour flotations at 114,000 × g the radioactive proteins persisted in the upper most

layers of the centrifuge tubes, and the specific radioactivity did not change significantly between the second and third runs. Radioisotope incorporation was inhibited by dinitrophenol and by *p*-fluorophenylalanine, known to be inhibitors of protein biosynthesis in other systems. Ninety-five per cent of the labeled proteins in the lipoprotein fractions were precipitated by 50 per cent saturated $(NH_4)_2SO_4$. The specific radioactivity of the proteins in the D < 1.063 fraction of the serum medium was 2.5 times that of the proteins in the D 1.063 - 1.21 fraction. Labeled lipoproteins with D <1.21 are also secreted into bicarbonate buffer, but in lower yield. Further chemical characterization of these lipoproteins is in progress.

9:10 Discussion

9:15

12. Aortic Phosphatide Synthesis in Hypercholesteremic and Normocholesteremic Atherosclerotic Rabbits

D. B. Zilversmit and E. L. McCandless. From the Division of Physiology, University of Tennessee, Memphis, Tenn.

Although in the rabbit atheroma phosphatide appears to be generated by arterial synthesis (Arch. Biochem. Biophys. **62**: 402, 1956), little or nothing is known about the causes of the disturbed metabolic state of the artery that lead to phosphatide accumulation in the lipid lesion. The present study was initiated for the purpose of ascertaining whether or not the presence of elevated serum lipid levels is required to maintain accelerated phosphatide synthesis in the artery. One group of rabbits was placed on 1 per cent cholesterol for 3 months and then on plain chow for 2 months (normocholesteremic), and another was treated in the reverse order (hypercholesteremic group). At the end of the 5 month period all animals received intravenous P^{32} for the study of arterial phosphatide synthesis. The serum cholesterol and phosphatide of the hypercholesteremic group were 2,150 and 750 mg. per cent, whereas the normocholesteremic serum concentrations were 120 and 125 mg. per cent respectively. The appearance of lesions in the aortas of the two groups did not differ significantly, however. The incorporation of P^{32} into phosphatides of the intima of the thoracic aorta was the same in both groups and was elevated several times above that found in the arteries of normal rabbits. Thus it appears that the mechanisms in the aorta that are responsible for the accumulation of aortic phosphatides may be initiated by hyperlipemia or hypercholesteremia in plasma but that, once set in motion, they are not easily stopped by a return to normal serum lipid levels.

9:25

13. Transport of Lipids from Calf Aortae to Blood

W. R. Nelson and N. T. Werthessen. From the Department of Physiology and Biochemistry, Southwest Foundation for Research and Education, San Antonio, Tex.

In the study of lipid transport in the aorta, a direct approach has been attempted. Using the aseptic in vitro perfusion of calf and baboon aortas as described by Werthessen et al. we have performed experiments on the following pattern: Whole blood was defibrinated 24 hours before use; 0.5 mc. of 1-C^{14}-acetate was added to 500 ml. of blood at the beginning of the perfusion. The perfusion was continued for 8 hours, and the then labeled blood was thoroughly and quickly washed out of the total system. Unlabeled blood was then added . The perfusion was continued for 24 hours. The C^{14} labeling of lipids in the aorta at the end of the perfusion and the labeled lipids in both bloods have been studied with the use of silicic acid columns and by direct isolation of individual lipids and classes of lipids. The results support the predictions of earlier studies in showing that cholesterol and other lipids move from the aorta into the blood. The degree and nature of the lipids involved in this movement will be reported in detail.

9:35

14. Turnover of Exogenous Cholesterol in the Artery Wall in Chickens

Seymour Dayton. From the Veterans Administration Center and the Department of Medicine, University of California, Los Angeles, Calif.

Cholesterol-4-C^{14} in tracer quantities was administered by gavage to a group of young adult White Leghorn cockerels that were on a normal diet, and the animals were killed at intervals ranging from 1 day to 42 days. Cholesterol was isolated separately from thoracic aorta, abdominal aorta, the paired brachiocephalic arteries, plasma, and liver, and was assayed for radioactivity. The main findings were the following: 1. Plasma cholesterol specific activities reached a peak at about 2 days. 2. Plasma ester cholesterol specific activity was lower than that of plasma-free cholesterol on the first day, and higher thereafter. 3. Specific activity of all artery cholesterol samples reached a peak at 8 to 9 days. 4. At the peak of its curve, the artery wall cholesterol specific activity was in each instance 50 to 80 per cent of the simultaneous plasma cholesterol specific activity. 5. Specific activity of abdominal aorta cholesterol rose and fell somewhat faster than that of thoracic-aorta and brachiocephalic-artery cholesterol. 6. Mean

values for cholesterol concentrations in the artery wall, in mg./Gm. of dry weight, were; abdominal, 7.2; thoracic, 9.3; brachiocephalic, 10.4. The difference between abdominal aorta and the other two samples was significant ($p < 0.01$).

These data demonstrate that the major part of the cholesterol of the artery wall in this species is derived from plasma cholesterol, but that other processes (presumably local synthesis) contribute a significant fraction. The findings of these experiments do not explain the difference in susceptibility of different arterial segments to cholesterol-induced atherosclerosis.

9:45 Discussion

10:00

15. Effect of Bile Acids and of Diet on Cholesterol Metabolism

E. H. Mosbach, L. L. Abell and E. Halpern. From the Columbia University Research Service, Goldwater Memorial Hospital and the Departments of Biochemistry and Medicine, College of Physicians and Surgeons, Columbia University, N. Y.

Although the prolonged oral administration of cholic acid (1.5 Gm./day) or deoxycholic acid (0.5 Gm./day) had no effect upon the serum lipid concentrations of human beings or of dogs, these substances inhibited the conversion of cholesterol to cholanic acids in dogs with bile fistulas. These results suggest that the cholanic acids influence both the synthesis and degradation of cholesterol in the mammalian organism.

Therefore, rates of cholesterol synthesis from acetate-1-C^{14} were measured in rats receiving cholanic acids in their diet and in animals not receiving supplements of these substances. Two basic diets were used: 1, a synthetic casein-sucrose diet and 2, a commercial rat chow. It was found that the nature of the basic diet profoundly influenced hepatic cholesterol synthesis. The administration of cholic acid or dehydrocholic acid consistently inhibited the incorporation of acetate-1-C^{14} into liver cholesterol, regardless of the composition of the basic diet. Cholesterol biosynthesis in the extrahepatic tissues (carcass) of the rats was not greatly influenced by a change of diet or by administration of bile acids.

10:10 Discussion

10:15

16. Mobilization of Lipids by Epinephrine

Karl E. Sussman, Eleazar Shafrir and Daniel Steinberg. From the Section on Metabolism, National Heart Institute, National Institutes of Health, Bethesda, Md.

The nature of the effect of epinephrine on serum lipids and their metabolism has not as yet been clearly established. Because of the possible implications with respect to atherosclerosis, and in the light of recent advances in lipid biochemistry, further exploration of the mechanisms and the controlling factors involved in the action of epinephrine was undertaken.

Epinephrine in oil (1 mg./Kg.) was injected subcutaneously into dogs. Fasting serum unesterified fatty acids (UFA), triglycerides, phospholipids and cholesterol were measured. Serum UFA rose within 1 hour after injection and reached peak values of 1.4 to 1.7 mEq./L., usually in 3 hours. Elevation of total serum lipids was first discernible at 6 hours. At 24 hours serum lipid had risen to 25 per cent above the control level, the elevation being primarily in the phospholipid and cholesterol-fractions. Similar responses were observed in epinephrine-treated rats. Triglyceride levels after epinephrine were related to the amount of fat in the animal's diet; in contrast to results obtained in dogs receiving low-fat diet, there was a considerable elevation in triglyceride levels in dogs fed a fat-rich diet. It was found that absorption of a fat load from the gastrointestinal tract was greatly prolonged in dogs receiving epinephrine. In control dogs the serum triglyceride level returned to normal within 4 hours after oral administration of cream containing 40 per cent butterfat (8 ml./Kg.); in the epinephrine-treater animals the triglycerides remained elevated for as long as 24 hours after the fat meal. Epinephrine did not inhibit the rate of disappearance of chylomicrons injected intravenously, which indicates that epinephrine does not interfere with the removal of fat from the blood stream once it has been absorbed.

Administration of glucose for several hours following epinephrine injection prevented the sharp initial rise in UPA concentrations. At 24 hours the UFA levels were no higher than in untreated animals. However, the glucose treatment did not prevent the rise in other lipids noted at 24 hours.

The possible relations, between the lipid-mobilizing effects of epinephrine described here and its calorigenic action, are under study and will be discussed.

10:25 Discussion

10:30

17. Lipemia in the Rabbit Following the Injection of Pituitary Extract

Daniel Rudman and Floyd Seidman. From the Columbia Research Service, Goldwater Memorial Hospital and the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y.

Treatment of hog, sheep, beef or human whole pituitary glands, or hog anterior pituitary lobes,

with M/10 Na_2HPO_4 yields an extract which regularly produces lipemia in the rabbit. A single subcutaneous injection causes a many-fold increase in the level of serum total lipids, including cholesterol and unesterified fatty acids. Serum lipid levels reach a maximum 18 hours after injection, and return to normal within 48 hours. The magnitude of the response shows a linear relationship to the logarithm of the dose. Electrophoresis studies show that the response on the first day consists largely of chylomicrons. When the lipemia is maintained by 3 daily injections, much of the serum lipid on the fourth day has the mobility of β-lipoprotein. Blood sugar content is unchanged during the period of lipemia.

Purified preparations of the 6 anterior pituitary hormones (growth, adrenotropic, thyrotropic, follicle-stimulating, luteinizing and lactogenic) have no significant effect upon the rabbit's serum lipids at dosages which contain at least 5 times the amount of each hormone present in a lipemia-producing dose of the crude extract. Amounts of the extract sufficient to produce lipemia in a rabbit have no demonstrable inhibitory effect upon the activity of lipoprotein lipase.

Acetone-dehydrated glands contain less than 30 per cent of the activity present in lyophilized glands. The active substance is heat-labile, nondialyzable, and precipitable by $(NH_4)_2SO_4$. It sediments in the ultracentrifuge at specific gravity 1.005. It can be adsorped upon, and eluted from, $Ca_3(PO_4)_2$gel.

10:40 Discussion

10:45

18. The Presence of the Direct Oxidative Shunt in Human Arterial Tissue

J. E. Kirk. From the Division of Gerontology, Washington University School of Medicine, St. Louis, Mo.

Determinations were made of the activities of glucose-6-phosphate dehydrogenase (G-6-P DH) and 6-phosphogluconate dehydrogenase (6-PG DH) in homogenates of human arterial tissue freshly obtained at autopsy. The measurements were performed by determining the rate of reduction of TPN by the homogenates, and using, respectively, glucose-6-phosphate and 6-phosphogluconate as substrate. The activity values for both enzymes were expressed as mM TPN reduced/Gm. wet tissue/hour.

The investigation revealed appreciable activities of both enzymes, indicating the presence of the direct oxidative shunt in human arterial tissue. The mean activity values for G-6-P DH observed for nonarteriosclerotic tissue samples from individuals aged 10 to 85 years were: aorta, 0.109 (N = 68); pulmonary artery, 0.078 (N = 67); and coronary artery, 0.090 (N = 27). The average activity of the arteriosclerotic aortic tissue was 67 per cent of the activity of the normal tissue, expressed on the basis of wet tissue weight (70 per cent when calculated on the basis of the tissue nitrogen content). The mean activity of arteriosclerotic tissue sections of the coronary artery was 79 per cent of the activity of the normal tissue, expressed on the basis both of wet tissue weight and tissue nitrogen content.

The activity of 6-PG DH in the arterial tissue was distinctly lower than that of G-6-P DH. Thus the mean activity values found for normal arterial tissue were: aorta, 0.011 (N = 53); pulmonary artery, 0.015 (N = 51); and coronary artery, 0.020 (N = 27). In the case of this enzyme the arteriosclerotic tissue sections of both the aorta and coronary artery showed activities which on the average were of the same order of magnitude as those observed for the normal tissue.

10:55 Discussion

11:00

19. Effect of Exogenous Estrogen on Rabbit Intraocular Atheromatous Aortic Homotransplants

A. C. Higginbotham and Francis H. Higginbotham. From the Department of Microanatomy and Organology, West Virginia University School of Medicine, Morgantown, W. V.

In addition to a protective effect, estrogens have been reported to promote regression of pre-established coronary, but not aortic, lesions in cholesterol-fed chicks (Pick et al., Circulation **6**: 858, 1952), but regression of both coronary and aortic lesions has been reported to occur in rabbits during estrogen therapy and of aortic lesions during testosterone therapy (Chakravarti et al., Indian J. M. Res. **44**: 683, 1956; Rossi et al., Minerva ginec. **5**: 295, 1953).

Due to the persistent hyperlipemia, atherogenesis proceeds for some time after cessation of cholesterol feeding (McMillan et al., Arch. Path. **59**: 285, 1955; Wilens and Gallo, Arch. Path. **64**: 570, 1957). It seems very probable that some regression of lesions, during estrogen therapy that has been instituted immediately after removal from cholesterol-supplemented diets, may result from inhibition of atherogenesis, from facilitation of regressive processes, or from both. Since the homotransplantation of atheromatous plaques into the anterior eye chambers of host animals immediately minimizes the progressive processes (Science **125**: 554, 1957), the effects of estrogen on the regressive processes may be more easily studied.

As a part of a program to study the effect of

estrogen on regression of pre-established plaques, an atheromatous aortic homotransplant was made into each anterior eye chamber of 2 male hosts and the left chamber of 2 others. Twelve days later each had implanted subcutaneously a 25 Mg. pellet of estradiol (Schering Progynon). Histologic study of 17- and 270-day transplants showed that regression had occurred, but that it differed in no significant manner from that described by the authors in similar transplants maintained in untreated hosts (Arch. Path. In press). Therefore it seems very probable that, in male rabbits at least, estrogens do not influence regression of atheromatous aortic plaques.

11:10

20. Induction of Atherosclerotic Infiltration in Intraocular Arterial Transplants

Meyer Friedman and Sanford O. Byers. From the Mount Zion Hospital, Harold Brunn Institute, San Francisco, Calif.

To determine whether lipid infiltration might occur in transplant of normal rabbit aorta placed in the anterior eye chamber of a rabbit made hypercholesteremic by dietary means, the following was done. Three segments of normal rabbit aorta were inserted into the anterior eye chamber of 16 rabbits. Seven of these rabbits then were made hypercholesteremic by feeding excess cholesterol, the remainder serving as controls. The segments were observed and photographed at various intervals. At the end of 6 to 8 weeks, approximately half of each group was killed, and the remaining halves after 12 weeks. The aortic transplants and the host's own aorta were studied histologically and chemically.

Transplants in hypercholesteremic rabbits exhibited gross differences, in situ, from those in the controls within 4 weeks. Moreover, on histological and chemical study, aortic transplants in the hypercholesteremic rabbits exhibited significant lipid infiltration and increase in cholesterol content at 6 to 8 weeks, and both phenomenon became very marked at the end of 12 weeks. This involvement differed from that occurring in the host's own aorta in several ways: 1. The lipid and cholesterol infiltration was 5 to 6 times more severe in the transplant. 2. The infiltration occurred in the adventitial portion of the transplant. No lipid infiltration occurred either at the 6- to 8-week or the 12-week period in the transplants placed in the control normocholesteremic animals.

These results appear to provide a new mode of inducing an atherosclerotic process that allows 1, direct continuous observation and photographic registration of the development of the process, 2, simultaneous comparisons of atherogenic processes taking place in intact and transplanted identical arterial tissues and 3, study of possible locally effective drugs and chemicals.

11:20 Discussion

11:30

21. Prevention of Experimental Cholesterol Atherosclerosis in Rabbits by an Oral Phenylpolysiloxane (DCF555)

Joseph M. Merrill and Frank Gollan. From the Veterans Administration Hospital, Nashville, Tenn.

The availability of a better silicone solvent, of low viscosity, water insoluble and practically inert physiologically, offered the possibility of studying its effect on experimental atherosclerosis of cholesterol-fed rabbits.

Groups of 6 rabbits were fed the following diets: stock diet, stock diet plus 2 per cent cholesterol, stock diet plus 2 per cent cholesterol with ≠2.0 per cent DCF555. Serum cholesterol and weights were determined weekly. At the end of 8 weeks the animals were killed and total tissue cholesterol was measured in the aorta and liver. The following final average cholesterol values were found. Stock diet animals, serum 52 mg. per cent; liver, 0.286 Gm. per cent; aorta, 0.134 Gm. per cent; change in weight, —12 per cent. Stock diet plus 2 per cent cholesterol-fed animals: serum, 1,369 per cent; liver, 1.754 Gm. per cent; aorta, 0.201 Gm. per cent; change in weight, —11 per cent. Stock diet plus 2 per cent cholesterol plus 2 per cent DCF555: serum, 316 mg. per cent; liver, 5.185 Gm. per cent; aorta, 0.141 Gm. per cent; change in weight, —19 per cent.

These results indicate that this silicone compound effectively prevented cholesterol accumulation in the aorta and to a lesser extent the anticipated rise in serum cholesterol, while the cholesterol content of the liver increased. DCF555 was more effective in preventing increases in serum cholesterol than 10 per cent linoleic acid in simultaneous experiments and 2 per cent nicotinic acid in previous experiments. The physical or chemical mechanism of this silicone compound on cholesterol absorption or synthesis is unknown.

11:40 Discussion

11:45

22. Rabbits on Carbohydrate-Cholesterol Diets

O. J. Pollock, Dover, Del.

Large amounts of carbohydrates (glucose, fructose, maltose, sucrose, corn starch, potato starch or rice) fed to rabbits for 2 weeks had no influence on blood cholesterol.

Combined diets of carbohydrates and cholesterol resulted in hypercholesteremia which was 40 per

ent higher than that induced by cholesterol feeding alone.

Upon termination of cholesterol diet the blood cholesterol of control rabbits fed chow returned to normal within 4 weeks. If, after the combined carbohydrate-cholesterol feeding period, carbohydrate diets were continued, the blood cholesterol not only failed to drop but rose within the first week by 25 per cent. After another week the blood cholesterol level was as high as at the end of the 2-week cholesterol intake. Subsequently, it took from 5 to 6 weeks for the blood cholesterol to return to pre-experimental level.

As yet, no significant differences in blood cholesterol levels at various dates during observation period were encountered between series of rabbits fed various carbohydrates. The influence of such diets upon animals fed cholesterol alone has not yet been studied. While all rabbits on the carbohydrate-cholesterol regimen had marked hepatic steatosis, the degree seemed to vary with the type of diet. The extent of aortic atheromatosis paralleled the maximum blood cholesterol level of the rabbits. There was no evidence of regression of aortic alterations in either series.

11:55 Discussion

12:00 ASSA Luncheon, Corinthian Room.
G. Lyman Duff Lecture, Arteriosclerosis and the Program of the American Heart Association.
George E. Wakerlin

SATURDAY AFTERNOON
CIVIC AUDITORIUM

2:00-5:00 p.m. Joint Panels on Arteriosclerosis with American Heart Association.

7:00-9:30 p.m. A.S.S.A. Members' Cocktails and Dinner, Veneto's Restaurant.

SUNDAY MORNING
CIVIC AUDITORIUM

Ivan D. Frantz Jr., Presiding

9:00

23. Reduction in Serum Cholesterol Levels by Nicotinic Acid (Including Studies Pertaining to the Mechanism of Action)

William B. Parsons, Jr., and John H. Flinn. From the Jackson Clinic, Madison, Wis.

Serum cholesterol levels in most hypercholesterolemic patients can be reduced by administration of large doses of nicotinic acid in the presence of a normal diet. The reduction is most prominent in the β-lipoprotein cholesterol fraction, with reduction of the beta/alpha$_1$ ratio. Nicotinic acid has been given in doses of 3 to 10 Gm. per day to 60 patients for periods of up to 2 years. Doses higher than 6 Gm. daily have not improved the results in refractory cases.

Flushing and pruritus subside rapidly in the early stages of therapy and have not interfered with therapy. No toxic effects have been observed on the hematopoietic, cardiovascular, renal, or hepatobiliary systems. A battery of 7 liver function tests in 19 patients and needle biopsies of the liver in 17 patients who had been treated for longer than 1 year revealed no abnormality of hepatic function or significant morphologic change. Dryness of the skin has occurred in 14 patients, 2 of whom have had a brown rash in the axillae, but these reactions have not interfered with continuation of therapy.

Nicotinamide is ineffective in reducing serum cholesterol levels. Differences in the action of this drug and nicotinic acid are being explored, in an effort to determine the mechanism of action of the latter. Studies of urinary levels of the pyridone derivative of N-methyl-nicotinamide are incomplete at the time of submission of this abstract, but indicate that only a small portion of the ingested nicotinic acid is excreted in this form. The possibility that the effective agent may be a metabolic product of nicotinic acid (perhaps nicotinuric acid or n-methyl-nicotinamide) is being investigated through a feeding of these compounds.

Preliminary studies of T-tube drainage in human beings suggest increased amounts of free cholesterol in the bile following nicotinic acid administration. Changes in bile acids have not yet been studied.

9:10

24. Studies on the Mechanism of Effects of Large Doses of Nicotinic Acid and Nicotinamide on Serum Lipids of Hypercholesterolemic Patients

O. Neal Miller, James G. Hamilton and Grace A. Goldsmith. From the Department of Biochemistry and the Nutrition and Metabolism Research Laboratory of the Department of Medicine, Tulane University School of Medicine, New Orleans, La.

Several reports have appeared which demonstrate that nicotinic acid but not niacinamide will lower the blood cholesterol level in hypercholesterolemic patients, but little is known of the mechanism of action. A natural-food diet was given, in which 20 to 25 per cent of the calories came

from mixed fats. The experiments were divided into 5 three-week periods: 1, control; 2, nicotinic acid, 2 Gm./100 lb. B. W.; 3, nicotinic acid plus DL-methionine, 4 Gm./100 lb. B. W. After 9 weeks both nicotinic acid and methionine were discontinued and niacinamide substituted (4), followed by another control period (5). The following observations were made: liver bracket, cholesterol (free and esterfied), phospholipid phosphorus, total esters and lipids in the blood. Urine was collected and assayed for nicotinic acid, niacinamide, N-methyl-nicotinamide, N-methyl-nicotinamide-6-pyridone, and nicotinuric acid. Stool collections were made during each period and the amount of sterols and bile acids was determined. When nicotinic acid was given alone or in combination with methionine, 40 to 50 per cent of the dose was excreted in the urine as methylated metabolites, and the remainder of the administered dose could be accounted for as nicotinic acid, nicotinamide and nicotinuric acid, the latter making up about 20 to 25 per cent of the total niacin metabolites excreted. As expected, the excretion pattern was different when niacinamide replaced nicotinic acid; N-methyl-nicotinamide excretion increased by 100 per cent, nicotinic acid and niacinamide excretion decreased by 80 per cent, and no nicotinuric acid was excreted. Only two-thirds of the administered niacinamide could be accounted for. Total cholesterol and total esters in the serum decreased during therapy with nicotinic acid during periods 2 and 3, but returned to control levels in period 4. The effect of nicotinic-acid therapy on the fecal excretion of bile acids and sterols will also be reported. The data suggest that nicotinuric acid may play a role in the metabolism of cholesterol.

9:20

25. Effect of Nicotinic Acid on Cholesterol Metabolism of the Rat

Charles H. Duncan and Maurice M. Best. From the Department of Medicine, University of Louisville School of Medicine, Louisville, Ky.

The incorporation of sodium acetate-1-C^{14} and of mevalonic acid-2-C^{14} into liver and serum cholesterol has been studied in the intact rat. The effect of nicotinic acid on synthesis of cholesterol and on its disappearance from serum and liver has also been studied.

Two hours after the intraperitoneal injection of sodium acetate-1-C^{14} in 4 rats, 0.164 ± .029 per cent of the administered C^{14} was present in liver and serum cholesterol. The addition to the diet of 1 per cent nicotinic acid for an 8 day period preceding acetate injection did not influence its incorporation into cholesterol, the mean being 0.163 ± .043 per cent.

The incorporation of mevalonic acid was much more efficient. Two hours after intraperitoneal injection in 4 rats, 5.14 ± 1.19 per cent of the injected activity was present as liver and serum cholesterol. Administration of nicotinic acid, 75 mg./100 Gm. body weight, by gavage 20 minutes before injection of the mevalonic acid, had no significant effect on incorporation of the latter into cholesterol, the mean being 5.85 ± .40 per cent.

Eight rats received intraperitoneal mevalonic acid and on the third through the sixth day thereafter were gavaged twice daily, the controls with water and the remaining 4 with nicotinic acid. On the seventh day the percentage of administered activity recovered in liver and serum cholesterol was 0.679 ± .066 in the control group and 0.68 ± .227 in the nicotinic acid group.

Since the addition of 1 per cent nicotinic acid to the diet of 24 rats for periods of 2 to 6 weeks resulted in a small but significant reduction in serum cholesterol, 64.5 ± 6.7 mg./100 ml. as compared to 76.4 ± 10.1 in a group of 20 control animals ($P < .01$), the incorporation of labeled acetate into liver and serum cholesterol of rats was studied after 6 weeks of feeding of 1 per cent nicotinic acid. In 4 control animals the incorporation was 0.174 ± .025, and in 4 receiving nicotinic acid it was 0.123 ± .038 per cent ($0.05 < P < .10$), suggesting decreased hepatic synthesis.

9:30 Discussion

9:45

26. A Comparison of Nicotinic Acid, Sitosterol and Safflower Oil in the Treatment of Hypercholesteremia

Kenneth G. Berge, Richard W. P. Achor, Nelson W. Barker and Marschelle H. Power. From the Mayo Clinic and Mayo Foundation and Graduate School, University of Minnesota, Rochester, Minn.

The effects of nicotinic acid administered orally and in doses of 1.5 to 6 Gm. daily to 59 persons with hypercholesteremia have been followed for periods of up to 3 years. In the absence of alterations in the diet, daily doses of 3 Gm. of nicotinic acid resulted in an over-all decrease in serum cholesterol of 17 per cent. A direct relationship between dose and degree of response was demonstrated. The treatment with nicotinic acid rarely is associated with severe side effects, and is practical to employ. Sitosterol and safflower oil were administered to 6 patients in whom the hypercholesteremia had been relatively resistant to nicotinic acid in a dose of 3 Gm. daily. Each agent including the placebo, was studied for periods of 3 months, and no alterations were made in the diet

during any phase of the study. Sitosterol was administered in a dose of 1 fluid ounce of a 20 per cent suspension before each meal or lunch, and safflower oil was given in a dose of 1 fluidounce 3 times daily. Determinations of plasma cholesterol were made at monthly intervals. The average cholesterol levels for the different periods were: placebo 363, nicotinic acid (6 Gm. daily) 293, sitosterol 323 and safflower oil 345.

In five of the 6 cases the simultaneous administration of sitosterol with an average daily dose of 4.8 Gm. of nicotinic acid resulted in a decrease of 21 per cent in the concentration of plasma cholesterol, whereas either agent used alone in the same dose resulted in a decrease of only 11 per cent. The effects of nicotinic acid and sitosterol therefore seem to be additive.

9:55

27. Changes in Serum Cholesterol on Supplementing The Diet With Cottonseed Oil or Completely Hydrogenated Coconut Oil

F. F. Mattson, J. C. Alexander, R. O. Carter and P. V. Newland. From the Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, O.

Twenty adult male human beings, in apparently healthy condition and with no indications of atherosclerosis, were subjects in an experiment in which the effect of supplementing the diet with a fat very high in polyunsaturated fatty acids (cottonseed oil) or very high in saturated fatty acids (completely hydrogenated coconut oil) was investigated. During the experiment the subjects consumed their regular diet but limited their food intake so as to maintain their initial body weight. The supplementary fat was administered at a level of 50 Gm. per day in the form of ice cream. During a 5-week period one half of the subjects received the cottonseed oil and the remainder received the coconut oil. At the end of this period the administration of fat received by each group was reversed, and supplementation was continued for an additional 5-weeks. Total serum cholesterol was measured at weekly intervals.

The supplementary dietary fat had no marked effect on the blood cholesterol level. With each subject as his own control, the serum cholesterol level was 98 per cent of that of the basal period while receiving the supplement of cottonseed oil and was 104 per cent of normal while receiving the coconut oil. Replacement of the cottonseed oil by coconut oil resulted in a 12 per cent rise in blood cholesterol level, while replacement of coconut oil by cottonseed oil resulted in an 8 per cent decrease.

10:05

28. Effect of β-Sitosterol and Unsaturated Vegetable Oil Combinations on Human Serum Cholesterol Levels

M. J. Fahrenbach, H. V. Lewry, B. A. Riccardi, C. W. Dunnett, J. C. Saunders, E. Lourie, J. Blodinger, J. M. Ruegsegger, W. C. Grant and T. H. Jukes. From the Nutrition and Physiology Section, Research Division, American Cyanamid Company, Pearl River, New York, and Rockland State Hospital, Orangeburg, N. Y.

Serum cholesterol values were determined at 14 day intervals over a 13 month period in 118 male patients, aged 17 to 54 years, in a mental institution; considerable individual fluctuations were observed. Following this pretreatment period the patients were randomly distributed into 5 equal groups according to ward location, serum cholesterol, age and body weight. Each group was placed on one of the following medications administered daily in 3 doses before meals: 1, control "candy bar" (milk solids, sucrose and flavoring) plus 7.5 Gm. corn oil; 2, 15 Gm. micronized β-sitosterol in "candy bar"; 3, 15 Gm. β-sitosterol plus 7.5 Gm. corn oil in "candy bar"; 4, 15 Gr. micronized β-sitosterol as a 20 per cent aqueous suspension; 5, 49 Gm. of an aqueous emulsion of a corn-safflower oil mixture (4:1) plus 1.65 Gm. β-sitosterol. This regimen was continued for 13 weeks. Groups 2, 3, 4 and 5 exhibited a significant drop in the average serum cholesterol values from an initial level of approximately 260 mg. per cent to 220 to 230 mg. per cent. Group 5 dropped more slowly but reached essentially the same level.

Following this 13 week period group 1 was given 15 Gm. β-sitosterol plus 7.5 Gm. corn oil in the "candy bar" and group 3 the control "candy bar" plus 7.5 Gm. corn oil. Simultaneously, medication was discontinued in groups 2 and 4 and the β-sitosterol was removed from the oil emulsion given to group 5. Serum cholesterol values were determined at the end of the second, third, and fourth weeks. The average cholesterol values of groups 2, 3 and 4 rose to pretreatment levels. Group 1 fell to about 235 mg. per cent and group 5 elicited an unexplained variable response (258, 235 and 248 mg. per cent.

All treatment was then terminated. During the following 6 weeks the cholesterol values of all 5 groups remained at pretreatment levels or higher.

10:15 Discussion

10:30

29. Thyroid Hormones and Lipid Metabolism: Effects of 3:5:3′-Tri-iodothyropropionic Acid on Serum Lipids in Hypothyroid and Euthyroid Patients

Marvin L. Sachs and Walter L. Arons. From the Department of Medicine, Hospital of the University of Pennsylvania, Philadephia, Pa.

The availability of new derivatives and isomers of thyroid hormones has stimulated the investigation of effects of these analogs on lipid metabolism. In this study, 3:5:3′-tri-iodothyropropionic acid (T_3-prop), a *thyroactive* compound of which 3 to 6 mg. daily maintain myxedematous patients euthyroid, was given to 4 hypothyroid and 6 euthyroid subjects after establishment of appropriate base lines. They were kept as far as possible constantly on their usual diets, and followed closely, with observations of weight, BMR, serum PBI, cholesterol, phospholipids, total esterified fatty acids, and lipoprotein electrophoretic patterns.

Among the hypothyroids, depression of the three lipid components measured occurred regularly on 2 mg. daily of T_3-prop, the fall being greatest with high base-line levels but being significant even when base-line cholesterols were less than 250 mg./100 ml. Cholesterol/phospholipid ratios decreased on treatment, impressively only when base-line lipid levels were high. On T_3-prop the BMR increased and weight decreased. By contrast, one hypothyroid patient given 45 mg. daily of 3:3′:5′-tri-iodothyronine, which seems not to be thyroactive, gained weight, maintained a low BMR and showed an increase in already elevated serum cholesterol and cholesterol/phospholipid ratio.

All euthyroid patients with base-line cholesterol levels over 250 mg./100 ml. showed significant depression of the lipids, without significant change in the cholesterol/phospholipid ratio, on 2 mg. of T_3-prop daily. This dose usually had no effect on the BMR of euthyroids, but 4 mg. daily tended to raise it slightly (within the euthyroid range) and to cause a small additional decrement in lipid levels. Some maintained constant weight and some lost, but weight change did not correlate with magnitude of serum lipid depression among euthyroids in this short-term study.

10:40 Discussion

10:45

30. Effects of Isocaloric Substitution of Carbohydrate for Dietary Protein on Serum Lipids and Lipoproteins and Their Response to Gonadal Steroid Administration

Robert H. Furman, R. Palmer Howard and Leonard N. Norcia. From the Cardiovascular and Endocrinology and Metabolism Sections, Oklahoma Medical Research Foundation and the Departments of Medicine and Biochemistry, University of Oklahoma Medical Center, Oklahoma City, Okla.

Little is known of the role of dietary protein in lipid metabolism and transport. The oft-cited correlation between "low" serum cholesterol levels and "low fat" diets in certain populations has diverted attention from the equally good correlation existing between the animal protein content of the diets and mortality from atherosclerotic cardiovascular disease.

A "complete" formula containing corn oil (40 per cent of calories), skim milk protein (14 per cent of calories) and glucose, supplemented with vitamins, iodine and iron, has been utilized under metabolic balance conditions, making possible total isocaloric substitution of glucose for protein.

Studies to date in 5 subjects indicate: 1. Substitution of glucose for protein in the formula results in reduction in serum cholesterol levels below that accountable for by the unsaturated corn oil of the protein-containing formula. 2. The cholesterol concentration is reduced relatively more than phospholipid. 3. The reduction in cholesterol and phospholipid concentrations is mainly in the β-lipoprotein fraction. 4. Replacement of sufficient dietary protein to establish nitrogen equilibrium increases serum cholesterol and phospholipid levels to those characteristic of the "complete" formula. 5. Testosterone administration during the protein-free diet period lowers both α- and β-lipoproteins (especially β) resulting in dramatic reduction in serum cholesterol and phospholipid levels. 6. Estrogen administration in the absence of dietary protein appears to have little additional effect on serum lipids or lipoproteins. Of interest is the finding that creatinuria does not result when methyltestosterone is administered in the absence of dietary protein.

The findings indicate that dietary protein may be an important factor in lipid metabolism and transport. They suggest that the effects of gonadal steroids on serum lipids and lipoproteins may be modified by alteration in dietary proteins.

10:55 Discussion

11:00

31. The Reactivity and Sensitivity of Human Peripheral Tissue in Fat Homostasis

E. H. Estes, Jr., M.D. Bogdonoff and D. Trout. From the Department of Medicine Duke Hospital and Medical Service, Durham Veterans Administration Hospital, Durham, N. C.

The intravenous injection of insulin and glucose is followed by a fall in the arterial level of nonesterified fatty acids (NEFA) and the obliteration of the negative arteriovenous difference normally observed. The observations of Bell indicated that a small dose of insulin injected into the femoral

artery is primarily fixed in the tissues of the injected extremity, exerting a greater effect on glucose metabolism in the injected leg than on areas outside of the injected extremity. The format of Hall's experiment provides a technic for the study of the effect of insulin upon fat homeostasis of peripheral tissues.

Normal fasting male subjects were studied in a resting state. Simultaneous arterial and venous samples were drawn from the lower extremities. Insulin (glucagon-free, 0.5 to 1 unit) was injected into the femoral artery of one leg. Samples were drawn 10 and 20 minutes following. Measurements were made of blood glucose, nonesterified fatty acids and cholesterol. In some cases heparin (2 mg.) was injected intra-arterially 10 minutes prior to the insulin administration.

The normal negative arteriovenous difference of NEFA was narrowed or reversed in the injected leg within 10 to 20 minutes. In the uninjected leg no such reversal occurred. These changes generally paralleled the effect observed in the levels of glucose. Cholesterol levels did not significantly change.

Heparin produced a rapid rise (within 10 minutes after injection) in NEFA level, more marked in the injected leg, but occurring as well in the uninjected leg. This rise was reversed by insulin injection.

These experiments indicate the importance and extreme sensitivity of the human peripheral tissues in the regulation of circulating levels of NEFA.

11:10 Discussion

11:15

32. Dietary Fat and Cholesterol Metabolism in Normal Subjects

Richard J. Jones and Michael F. Golden. From the University of Chicago, Chicago, Ill.

To study the influences of the quality and quantity of dietary fat on the rates of synthesis and excretion of cholesterol, 4 normal male students were observed in a metabolic ward on diets of natural foodstuffs. After 3 weeks of an unchanging diet containing 150 Gm./day of only animal fat, C^{14}-acetate was injected intravenously and the specific activity and concentration of the serum cholesterol were observed from 4 hours to 18 days. The diet was then altered to contain 100 Gm./day of animal fat. In the case of one subject, 50 Gm./day of corn oil was added, while in the others caloric balance was maintained by supplemental carbohydrate. Cholesterol intake was maintained constant by the addition of crystalline cholesterol. A second dose of C^{14}-acetate was injected intravenously after an adjustment period, and again the time course of the concentration and specific activity of the serum cholesterol was followed for 3 weeks.

Each subject showed a fall in serum cholesterol consequent to this modest reduction in animal fat; the subject receiving the corn oil supplement had a higher and more stable initial level of serum cholesterol and also demonstrated a sustained reduction. All subjects showed a total increase in cholesterol synthesis, as suggested by the peak specific activity of free cholesterol at 4 hours, with a lower level of animal fat in the diet. The decrease in mean serum cholesterol was also accompanied by an increased turnover rate of serum cholesterol, as suggested by the biological decay curve.

11:25

33. The Effect of Dietary Cholesterol Upon the "Synthesis" of Plasma Cholesterol in the Human

George E. Cox, Marjorie Counts, Joanne Wolski, Juana Alvarez and C. Bruce Taylor. From the Department of Pathology, Presbyterian-St. Luke's Hospital, Chicago, Ill.

To test the concepts that 1. endogenous synthesis of plasma cholesterol occurs chiefly in the liver, and 2. such synthesis can be relatively quantitated by measuring the uptake of C^{14}-sodium acetate into plasma cholesterol, 7 healthy adult human volunteers ingested a moderately low cholesterol diet for a year or longer. Subjects GC, BT and NY (see table) then ingested a cholesterol-free diet for 6 weeks; subjects SC, JC, MC and DK ingested a very low-cholesterol diet for 3 weeks and a cholesterol-free diet for 1 week, prior to their first administration of C^{14}-acetate. Later the latter 4 subjects ingested for 1 week a diet including 6 Gm. cholesterol and 20 Gm. butter daily, prior to their second administration of C^{14}-acetate. In each case the dose of acetate was 8.2 mg. NaAc with 100 mc. C^{14}, administered orally and in water to subjects in a fasting state, with no food intake for 2 hours after. The table shows the apparently typical responses of dogs and monkeys, both animals showing marked suppression of acetate uptake following cholesterol feeding. However, only 1 human being showed any significant suppression, and 2 showed definite increases in the acetate uptake following the feeding of cholesterol and fat. This and additional similar data support the hypothesis of a marked species difference between human beings and lower animals regarding the uptake of acetate into plasma cholesterol.

Subject	Specific activity of serum total cholesterol 4 hours after acetate ingestion* DPM/mg. cholesterol			
	Cholesterol-free diet		Cholesterol-rich diet	
Dog 68	178	(170)	—	—
Dog 52	—	—	7	(380)
Monkey 61	372	(165)	—	—
Monkey 8	—	—	38	(765)
GC	266	(143)	—	—
BT	111	(204)	—	—
NY	87	(227)	—	—
SC	165	(165)	232	(223)
JC	155	(134)	97	(175)
MC	153	(205)	373	(198)
DK	283	—	266	—

*The corresponding serum total cholesterol values (mg. %) are in parentheses.

11:35 Discussion

11:45

34. Reduction of the Level of Serum Cholesterol in Man by Neomycin

Paul Samuel and Alfred Steiner. From the Research Service, First (Columbia University) Division, Goldwater Memorial Hospital, Department of Hospitals and the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y.

During the course of a clinical study on the effect of various fats upon serum lipids of a group of patients having coronary atherosclerosis, it was observed that the oral administration of neomycin to a patient with an intercurrent salmonella infection was associated with a decrease in the serum cholesterol level. Additional observations have been carried out in 10 patients following the daily oral administration of 0.5 to 2 Gm. neomycin (Mycifradin Sulphate®) for periods of up to 2 months. The results revealed a decrease in the serum cholesterol level in each patient that varied from 20 per cent to 25 per cent. The medication was well tolerated. A mild, easily controlled, transitory diarrhea occurred in 4 patients.

The mechanism of action of neomycin in lowering the level of serum cholesterol is not understood. However, studies are in progress in an attempt to elucidate these observations. The effect of other antibiotics on the serum cholesterol level is also being investigated.

11:55 Discussion

SUNDAY AFTERNOON
CIVIC AUDITORIUM

Aaron Kellner, Presiding

1:30 p.m. President's Address
R. Gordon Gould

2:00

35. The Lipid Content of the Abdominal Aorta in Overweight and Underweight Men

J. C. Paterson and Jean Mills. From the Clinical Investigation Unit of Westminster Hospital, Department of Veterans' Affairs, and the Collip Medical Research Laboratory, University of Western Ontario, London, Canada.

Two interim reports have already been made to the Society on a long-term study in which the serum lipid levels estimated serially during life in 800 permanently hospitalized male patients have been compared with the severity of atherosclerosis in fatalities in the series. No significant relationships have yet been established (in the first 120 fatalities) between the antemortem serum lipid levels (total serum cholesterol, cholesterol phospholipid ratio, atherogenic index) and the severity of atherosclerosis. These results will be presented briefly.

Certain possible fallacies in our methods of evaluation in this continuing project are being studied. One of these is the subject of the present report, viz. Is terminal loss in body weight from wasting disease associated with a resorption of lipid from atherosclerosis plaques?

The nutritional state of each of the 120 fatalities has been compared with the lipid content of the intima of the abdominal aorta. The desirable weight was estimated from the length of the body by use of the Metropolitan Life Insurance Company Table of Desirable Weights for Men (1951). The actual body weight was obtained by weighing the body prior to autopsy (with a correction for hydrothorax and ascites). The lipid content of the aorta was obtained by estimating the total extractable lipid in its abdominal portion.

The data on 43 fatalities aged 60 to 69 years, and on 49 fatalities aged 70 to 79 years, have been analyzed separately. In neither age group was any significant relationship found between the nutritional state and the amount of extractable lipid in the abdominal aorta. The data for other age decades were unsuitable for analysis. The results do not support the contention that the lipid in

atherosclerotic plaques is resorbed in the course of lasting disease processes.

2:10

36. Atherosclerosis in Obese Patients at Autopsy

James C. Roberts, Jr., and Robert H. Wilkins. From the Department of Pathology and the Addison H. Gibson Laboratory of the University of Pittsburgh School of Medicine, Pittsburgh, Pa.

Detailed gross morphological studies of all the routinely accessible arteries in 500 consecutive adult autopsies have been made with the use of a grading system which incorporated both the extent of intimal involvement and the severity of individual lesions. Height-weight indices were calculated for all patients according to the Quetelet-Bouchard formula, and the heaviest 16 per cent and thinnest 16 per cent of both males and females were separated for further study. Adjustments of weight were made for peripheral edema, ascites and hydrothorax. All groups were then subdivided according to presence or absence of both morphological and clinical criteria for hypertension, and their group atherosclerosis profiles were compared.

Forty-seven obese males had more coronary atherosclerosis (and more old or recent infarcts) than did 47 thin males, but there was no significant difference in the extent and severity of atherosclerosis elsewhere in the body. Thirteen hypertensive obese males had no more atherosclerosis than 34 normotensive obese males, but had a slightly higher incidence of atherosclerotic catastrophes. Thirty obese females had more atherosclerosis in every site than did 30 thin females, and had more atherosclerotic catastrophes; but in contrast to the males, in whom hypertension played little obvious role, almost all the additional atherosclerosis and atherosclerotic catastrophes were in the 13 of the obese females who were also hypertensive.

Profiles of the distribution of atherosclerosis in the several groups will be presented and correlated with the clinical and morphological findings.

2:20 Discussion

2:30

37. Human Endogenous Lipemia Clearing Activity—Observations in 482 Individuals

H. Engelberg. From the Cedars of Lebanon Hospital, Los Angeles, Calif.

During the past 3 years the plasma of 482 people has been tested for endogenous lipemia clearing activity (CF) using a coconut oil substrate. In most subjects one observation was made, but in approximately 100 patients the plasma was tested on several occasions. Endogenous CF was found in 112 of the 482 individuals, an incidence of 23 per cent. A lower percentage of positivity, perhaps 10 to 15 per cent, would have been obtained if only one plasma sample had been tested for CF. When CF was found on the first examination, it was more apt to be present on repeat tests, but not necessarily. When it was absent initially, it was more likely to remain so, but again this was not always true.

No age or sex difference in incidence was found except in the case of individuals of over 80 years, in whom plasma CF was present in the majority. There was no difference in the average cholesterol levels (364 patients) between the group with and without CF (255: 261), but the S_f 0-12 lipoproteins (234 patients) were lower in the group with CF (456: 496), and the S_f 12-400 lipoproteins (234 patients) were significantly lower (195: 257). Frequently, however, CF is absent when lipoproteins are low, and infrequently it is present with elevated lipoproteins. In 76 of the 112 people with CF the effect of inhibitors or of tricalcium phosphate absorption was evaluated. In 69 of the 76 the inhibition or adsorption characteristics of endogenous plasma CF were identical with those of post-heparin clearing activity (lipoprotein lipase). In 32 subjects (with and without CF) lipolytic activity was determined by glycerol release studies. It is apparent that lesser degrees of lipolysis may occur without optical density changes, and that CF which did not show the inhibition or adsorption characteristics of lipoprotein lipase was usually not lipolytic.

2:40

38. Lipemia Clearing Factor Activity in Coronary Heart Disease

Martin F. McDowell, Alick Little and Henry M. Shanoff. From the Department of Veterans' Affairs, Sunnybrook Hospital, Toronto, Ontario, Canada

According to several reports in vivo lipemia clearing factor activity is decreased in patients with coronary heart disease. However, fully quantitative methods have not been applied, and the activity of this enzyme has not been correlated with the concentrations of serum lipid fractions.

Accordingly, plasma clearing factor activity was measured, by a simplification of a quantitative in vitro technic (Circulation **15**: 889, 1957), in coronary and control patients. The maximum rate of change of optical density in the test system during 10 minutes gave reproducible results in agreement with those of the original method.

The subjects were 75 males between the ages of 30 and 55. The coronary patients were survivors of proven myocardial infarcts. The controls were divided into groups, with and without a family history of atherosclerosis.

	No.	Mean clearing factor activity
Control group	45	.143 ± .012
Negative family histories	24	.155 ± .017
Positive family histories	21	.130 ± .016
Coronary group	30	.104 ± .012

The difference between the coronary group and the controls with a negative family history was significant ($p = < .01$). The difference between the coronary group and the combined control group was also significant ($p = < .05$). Only 3 men were found who had virtually no clearing factor activity, and all were in the coronary group. There was no correlation of clearing factor activity with serum total, free and ester cholesterol, serum phospholipids, C/P ratio or fasting plasma optical density. The correlation between clearing factor activity and serum neutral fat and standard S_f 0-400 lipoprotein fractions also will be presented. Spontaneous clearing factor activity was shown to be present.

2:50

39. Lipoprotein Lipase in Blood Plasma of Men with Coronary Heart Disease

Richard J. Havel and Martin Peterson. From the Department of Medicine, University of California School of Medicine, San Francisco, Calif.

The study was undertaken to examine the hypothesis that deficiency of lipoprotein lipase is related to the genesis of coronary heart disease. Lipoprotein lipase activity in postabsorptive blood plasma of 20 men with established coronary heart disease (group 1), mean age 49, has been compared with that of 20 men of comparable age without evidence of vascular disease (group 2). Versenated blood samples were obtained prior to, and 5 min. after, intravenous administration of heparin (2 mg./m² BSA), chilled, and centrifuged at 3 C. Assays were carried out promptly. Plasma was incubated at 25 C. with 1/10 volume of 1 per cent coconut oil emulsion. Enzyme activity was assayed by decrease in optical density of substrate and by production of unesterified fatty acids (UFA). For post-heparin samples a rate constant (k) was calculated for the period of linear decrease in optical density as ΔOD units/min. × 10^3. UFA production after heparin was linear during the incubation period of 30 min. No significant difference in ΔOD or ΔUFA was observed between the 2 groups prior to heparin. After heparin, k was lower in group 1 (11.2 vs. 13.0: $.025 > p > .01$), but ΔUFA was not (group 1, 1.33 and group 2, 1.31 μEq./ml.). The 2 measures of enzyme activity correlated poorly. Neither measure correlated with plasma UFA, total cholesterol, phospholipid or triglyceride concentration. UFA concentrations were similar in the 2 groups (group 1, 0.55 and group 2, 0.54 μEq./ml.), but triglyceride concentrations were higher in group 1 (159 vs. 112 mg./100 ml.: $.025 > p > .01$. Under the conditions of this study no evidence was found for deficiency of lipoprotein lipase in subjects with coronary heart disease. Assay by measurement of optical clearing of substrate did not provide a valid measure of enzyme activity.

3:00 Discussion

3:15

40. Environmental Factors Influencing Blood Clotting—Their Effect on Long-Term Anticoagulant Therapy

George A. Mayer and W. Ford Connell. From the Department of Medicine, Queen's University, Kingston, Canada

200 patients, most of them having coronary disease, were followed during anticoagulant therapy for ½ to 4 years. Therapy was controlled solely by the authors' Standard Clotting Time. Results were excellent: no thromboembolism or hemorrhage occurred when the test was in the therapeutic range. This technic has the added advantage of enabling study of the clotting time over long periods. As a rule, therapy became stabilized in 6 to 10 weeks; thereafter control was usually steady. As is well recognized, acute intercurrent disease and certain drugs upset the clotting time. In addition, fluctuations were noted which we have correlated with other environmental factors:

1. During emotional upset, the clotting time was sometimes observed to change radically. Depressive or anxiety states tend to shorten, elation to lengthen, the clotting time.

2. In unpublished experiments, we found no significant change in clotting time when the diet of healthy young persons was considerably changed in respect of dietary fat. However, we placed 9 coronary subjects, during anticoagulant therapy, on low animal fat—high corn oil diets. In all, after several weeks, clotting time rose sharply and the maintenance dose of anticoagulant required marked reduction. The final maintenance dose approximated 50 per cent of the former requirement.

3. Further unexpected fluctuations were noted to correlate significantly with sudden changes in barometric pressure: a noticeable rise in pressure lengthened and a fall shortened the clotting time.

These observations are important in long-term anticoagulant management. Their application should reduce the incidence of thromboembolism and hemorrhage during such treatment.

3:35

41. Coagulation Changes During Alimentary Lipemia in Subjects with and Without Atherosclerosis, and the Effect of Various Lipids

J. F. Mustard. From the Department of Medicine, University of Toronto and the Department of Veterans Affairs, Sunnybrook Hospital, Toronto, Canada

During alimentary lipemia susceptible individuals show blood-clotting changes which are interpreted to mean increased intravascular activity of the thromboplastin mechanism. These changes are a decrease in platelets, antihemophilic globulin (AHG) activity and increase in Christmas factor activity. The changes were studied in male subjects divided in groups as follows: clinical atherosclerosis under age 50, group 1; over age 50, group 2; no clinical atherosclerosis but a positive family history, group 3; no clinical atherosclerosis and a negative family history, group 4.

Group 1 had the greatest increase in Christmas factor activity and decrease in AHG activity during lipemia. They also had some reduction in platelets. Group 4 showed the least change in these indices. Groups 2 and 3 showed equal degrees of change, nearly as great as for group 1. Subjects with clinical atherosclerosis or a positive family history showed greater in vivo coagulation changes during lipemia than subjects with no family and no personal history.

The effect of different lipids on blood coagulation in vitro and in vivo were studied. Butter was as active as platelets in the thromboplastin generation test. Margarine, corn oil and cod liver oil were inactive. Addition to butter of material containing phosphatidyl serine inhibited the activity of butter, whereas adding material containing phosphotidyl ethanolamine to margarine made margarine as active as butter. In in vivo studies, butter most accelerated the thromboplastin mechanism. However, a meal of butter and material containing phosphatidyl serine caused no acceleration, whereas a meal of margarine and material containing phosphatidyl ethanolamine did. The accelerating effect of lipids on clotting varies with the nature of the lipid.

3:45 **Discussion**

3:45

42. A Study of the Histogenesis of Atherosclerosis in Man

Robert W. Wissler, Merle S. Moskowitz, Randolph H. Hughes and Lorraine G. Petrie. From the Department of Pathology, University of Chicago, Chicago, Ill.

For a better understanding of how atherosclerosis begins, standard blocks have been prepared from the aorta and coronary arteries obtained from 100 consecutive autopsies on patients aged between 6 days and 83 years. The grossly *least involved* portions of the first 7 cm. of the ascending thoracic aorta and the first 3 cm. of anterior descending coronary arteries were imbedded in carbowax, and adjacent sections were stained for fat, fibrin, acid mucopolysaccharide, collagen, elastic tissue and smooth muscle. Gross numerical quantitation of the extent of atherosclerosis of other areas of these vessels was also obtained, so that the microscopic findings could be interpreted in terms of over-all susceptibility of the individual to the atheromatous process.

Of the 50 cases that have been evaluated to date, fatty change is by far the most common alteration revealed microscopically in the early lesions. It has been present in varying degrees in 38 of the 50 aorta samples and in 36 of the coronary samples. In general, the fat accumulation was more severe in the segment of coronary artery than in the segment of ascending aorta. Material with tinctorial characteristics of fibrin has not been identified in any of these vessels and positive staining for acid mucopolysaccharide, when present, usually appeared to be diffusely distributed in the vessel wall and unrelated to early plaques. Focal intimal or subintimal staining for acid mucopolysaccharide was seen in 20 of the aortas and 29 of the coronary arteries. In general, it did not correlate as well as sudanophilia did with severity of disease, as judged either by intimal thickening or gross grading.

These microscopic findings will be correlated in the completed series with age, sex, gross grading and other selected clinical and pathological observations.

3:55

43. The Problem of Thrombosis in Atherosclerosis

Ira Gore, Veterans Administration Hospital, West Roxbury, Mass. From the Department of Pathology, Harvard Medical School, and the Department of Nutrition, Harvard School of Public Health, Boston, Mass.

The tendency of thromboses to occur in atherosclerotic vessels is one of the prineiple hazards of the vascular disease. Studies of the coagulative mechanism have suggested that transient or persistent elevations of blood lipid may (Sohar et al., 1957) or may not (Manning and Walford, 1954) result in increased coagulability and thrombosis. In this regard at least, there seems to have been little consideration of the possibility that constituents of the vessel wall contribute to the fluidity of the blood.

The ground substance of the aorta (and presumably of other vessels) is acid mucopolysaccharide in nature and is composed of chondroitin sulfate (Meyer, 1954). Its polysaccharide nature, sulfation, and anionic character relate it (chondroitin sulfate) to heparin; and indeed it has an anticoagulant activity 30 to 45 per cent of that of heparin (Foster and Huggard, 1955). If this constituent of the vessel wall is physiologically influential in maintaining the fluidity of the blood, one may well wonder whether the propensity of thromboses to occur in atherosclerosis may not be due to an interference with this mechanism.

A series of whole aortas was stained with Alcian blue. The latter has been shown to be a selective histologic stain for acid mucopolysaccharides (AMP) (Mowry, 1956). In normal segments there is a diffuse pale blue coloration of the intact intima. Precisely coincident with superficial deposits of subintimal lipid, so-called lipid streaks, previously demonstrated with sudan, there are striking increases of AMP as indicated by the intensity of the blue stain. More advanced elevated plaques which roughen the surface and contain deep-lying deposits of lipid, as well as plaques with calcium or hemorrhage, stain faintly or not at all with the dye. These, it will be recognized, are the types of intimal lesion that are associated with clinical disease because of the frequency of complicating thrombosis. On the other hand, lipid streaks, which contain an abundance of AMP, have no clinical significance other than to provide the background upon which more advanced atherosclerotic lesions form.

4:05 Discussion

4:15

44. A Ten-Year Follow-up of a Large Kindred in Which Essential Familial Hypercholesterolemia is Present

Winnifred Seegers, Richard C. Bozian, Ira J. Lauffer, John F. Heffernan and Chas. F. Wilkinson, Jr. From the New York University Post-Graduate Medical School, New York, N. Y.

A large kindred with essential familial cholesterolemia was reported in 1948. This report is concerned with a 10-year follow-up of this group.

Intensive studies were carried out on each member of the kindred who was available and cooperative. This report will only concern the data that bear on the increase with age of total blood cholesterol and on the use of the level of the total blood cholesterol in differentiating between the heterozygous hypercholesterolemic and the normocholesterolemic.

Over 100 patients studied 10 years ago were restudied. Many births since 1948 have added data that is valuable in the understanding of the genetic transmission of this trait, Our data indicate that some of the assumptions and conclusions reached in the 1948 report should be modified.

There was an average increase in the total blood cholesterol. However, this increase is not great and does not appear predictable.

The cutting point between the normocholesterolemic and heterozygous abnormal does not appear to be as sharp as it did on the first survey. Our data indicate that there is a range in which the normocholesterolemic cannot be identified positively. This range is relatively narrow and does not invalidate the previous conclusion as to the mode of genetic transmission.

4:25 Discussion

TO BE READ BY TITLE

45. Influence of Salts of Nicotinic Acid on Serum Cholesterol in Man

R. Altschul and A. Hoffer. From the University of Saskatchewan, Saskatoon, Canada

Altschul, Hoffer and Stephen have found that large doses of nicotinic acid (1 Gm. or more/50 lb. body weight) lower the serum cholesterol in normal and sick people. Altschul has also shown that in rabbits nicotinic acid lowers serum cholesterol and inhibits cholesterol arteriosclerosis. These findings have been confirmed for human beings repeatedly, and for rabbits by Merrill and Lemley-Stone. In a few patients, however, the administration of these high doses was followed by gastrointestinal disorders, and in still fewer cases (3 out of 45, Achor et al.) the treatment had to be discontinued. This poor tolerance may be due either to a specific action of nicotinic acid or to its acidity (pH 3.3). In 1939 Unna pointed out that in animals such gastrointestinal disturbances can be avoided by replacing the acid with its sodium salt. Nothing was known then of the cholesterol-lowering effect of nicotinic acid. To ascertain whether salts of nicotinic acid lower serum cholesterol as well as the acid does, we gave nicotinic acid, buffered with sodium bicarbonate (or sodium and potassium bicarbonate) to normal human beings, some of whom had been tested previously with nicotinic acid. Fifty Gm. nicotinic acid and 32 Gm. bicarbonates are completely soluble in 500 ml. water making a solution with a pH of approximately 6.2. Ten ml. of this solution corresponded to 1 Gm. nicotinic acid and should be diluted prior to being taken. The lowering of serum cholesterol by these buffered solutions corresponded to that following the use of nicotinic acid.

46. Experimental Cholesterolosis and Lipidosis. Effect on Free and Bound Cholesterol and Lipid-Phosphorus Content of Rabbit and Rat Adrenals, Aortas, Heart Muscles and Plasmas

Clifford A. Angerer, Jay W. Constantine and Florence Kraft. From the Department of Physiology, Ohio State University College of Medicine, Columbus, Ohio.

These biochemical analyses were undertaken as a sequence to our previous studies on the oxidative metabolism of aortas and heart muscles of rabbits and rats following experimental cholesterolosis and lipidosis. Young male rabbits and rats were divided into 5 dietary groups: 1, normal; 2, 1 per cent cholesterol in 10 per cent cottonseed oil; 3, cottonseed oil; 4, 1 per cent cholesterol in 10 per cent ether (evaporated); and 5, ether (evaporated). Rabbits and rats were fed the indicated regimen for about 8 to 10 weeks. Cholesterol was determined by the Sperry-Schonheimer method, lipid phosphorus by the Youngsburgs modification of the Fiske and Subbarrow method. The following data were obtained from a comparison of the indicated dietary groups. For a given tissue all data are presented as the per cent difference between free and bound cholesterol, lipid phosphorus and C/P ratio, respectively.

Comparison 3-1. Rabbits: adrenals 59, −2, 0, 0; aortas −9, −100, −33, −10; hearts 0, 0, −37, 39; plasmas −39, −26, −49, 35. Rats: adrenals −20, −1, −18, 18; aortas 0, −6, −25, −1; hearts −7, −100, −25, −1; plasmas 4, 1, −1, 3.

Comparison 2-3. Rabbits: adrenals 211, 188, −13, 216; aortas 1095, 350, 150, 1424; hearts 69, 14, 0, 176; plasmas 2,000, 2,540, 832, 354. Rats: adrenals −5, 12, 7, 15; aortas 14, −67, 0, 27; hearts 8, 1, 0, 27; plasmas −5, 16, −2, 18.

Comparison 5-1. Rats: adrenals −38, −7, −29, 36; aortas 9, −57, −50, 89; hearts 0, 0, −25, 47; plasmas −67, −8, −23, 46.

Comparison 4-5. Rats: adrenals −9, 24, 17, 0; aortas −4, −33, 0, −4; hearts 0, −100, −17, 1; plasmas −18, −1, 12, −17.

The analyses for the last 2 comparisons of rabbit tissues are nearing completion and these data will be presented and discussed.

47. Reliability of an Autopsy Series for Epidemiological Inferences

W. Beadenkopf, A. K. Polan and A. Daoud. From the New York State Department of Health and Albany Medical College, Albany, N. Y.

A series of autopsied patients make up the population base for a pathological-epidemiological study of coronary artery atherosclerosis. Special efforts are made to measure the amount of coronary artery atherosclerosis and to determine from several sources, chief of which is an interview with a relative or close friend, some background living characteristics about the individual. Associations will be sought in these 2 sets of data.

The study population (autopsied patients 15 years of age and older) is compared in regard to several characteristics with 1, all deaths that occur in the 700-bed general hospital (rate of autopsy, 65 per cent) and 2, all deaths recorded in Albany County. The study population is very similar to the hospital death population in respect of age and sex distribution, marital status, nativity, and most of the disease groupings as to cause of death. The autopsy consent rate (35 per cent) for Jewish persons was approximately one half of that for Protestants and Catholics.

The study population differs from all deaths recorded in the county in that in the study group there are 1, a smaller proportion of females 75 years of age and over, 2, a slightly higher proportion of married individuals and a lower proportion of widowed, and 3, a higher proportion of deaths assigned to cancer and a lower proportion to arteriosclerotic heart disease.

We conclude that autopsy series may be employed for the study of selected epidemiological characteristics. For each association under study, however, search should be made for bias and caution be employed in drawing inferences.

48. Hypertensive Aortic Disease

John R. Caldwell. From the Division of Hypertension, Department of Medicine, Henry Ford Hospital, Detroit, Mich.

Many middle-aged or elderly patients have fluctuant blood pressure elevations, aortic dilation and elongation of chest x-ray and no sign of serious disease. However, some have had arterial insufficiency or thrombosis and are regarded as having arteriosclerotic hypertension.

Aortic dilation and elongation were found in 112 of 355 patients having hypertension of 150/90 or above. Paralleling an increasing incidence of aortic ectasia with increasing age is an increase in ischemic arterial disease. Also found to increase with age were the levels of casual systolic blood pressure and wide fluctuations of blood pressure both systolic and diastolic. Twenty-two per cent of those with hypertension and aortic ectasia had clinically significant focal episodes of ischemic arterial disease (either thrombosis or insufficiency in cardiac, intracranial or peripheral areas).

Ischemic arterial disease was present in 41 of the 355 hypertensive patients. The average age for these 41 was 60 years, their average casual blood pressure was 194/110, average basal blood pressure 142/80, indicating a fall of 30 mm. Hg in

diastolic pressure under resting conditions. Sixty per cent of this group had aortic ectasia.

Signs of severe hypertensive disease were present in 42 patients. Here a striking, direct relationship to the levels of basal diastolic pressure was evident, but no correlation with increasing age. Ischemic arterial disease shows no such relationship to the height of the resting diastolic pressure, but shows a good correlation with age. Aortic ectasia correlates well with age and with pressure.

Transient blood pressure elevations or fluctuant blood pressure from any cause may result in a dynamic elongation and dilation of the aorta and major arteries.

This could also be a physical force of importance in accelerating atherosclerotic disease.

According to clinical experience, hypertensive aortic disease is not incompatible with a normal life expectancy and is benign unless a serious atherosclerotic complication occurs.

49. Some Pathologic Aspects of a Pathological and Epidemiological Study of Coronary Atherosclerosis

A. Daoud, A. W. Wright, and W. Beadenkopf. From the Department of Pathology, Albany Medical College and the New York State Department of Health, Albany, N. Y.

A preliminary report of pathologic findings obtained during a continuing pathological and epidemiological study of coronary heart disease, conducted jointly by the New York State Department of Health and the Department of Pathology of the Albany Medical College, will be presented. Adult individuals dying of any cause and coming to autopsy in the Albany Hospital were the source of the material. In each case special examination of the heart and its blood vessels was made, the arteries in particular being subjected to detailed study. The standard procedure consisted of making a series of cross sections of the coronary arteries at approximately 5 mm. intervals, and with a caliper measuring accurately the inner and outer diameters of the vessels at varying numbers of the cut sites. These measurements, as well as a notation of the presence of such abnormal changes as intramural hemorrhage, ruptured plaque, thrombosis, etc., were recorded on a diagram and chart. From the arterial measurements the average thickness of the walls of the coronary arteries was calculated in a manner to be described in detail. This average is considered to represent a quantitative expression of the atherosclerotic process as it affects the coronary artery system. Analyses designed to demonstrate the degree of reliability of these procedures, as well as the relation of the average thickness of the coronary artery walls to age, sex, the presence of thrombus formation, and other pertinent pathologic and clinical conditions associated, or suspected of being associated, with atherosclerosis, such as myocardial infarction, angina, diabetes mellitus, etc., will be presented.

50. The Influence of Saturated Fatty Acids on Blood Coagulability

Herbert L. Davis and Nora L. Davis. From the Departments of Biochemistry and Surgery of the University of Nebraska College of Medicine, Omaha, Neb.

The slow deposition of lipid-rich aggregates in and on vascular tissues reveals a pathologic lowering of the normal colloidal stability of all the blood components, with special regard to the lipids involved in the least stable ones. Such deposits may, alone and in themselves, lead to insignificant effects, since collateral channels are established to provide adequate supply and distribution of blood for heart, brain, and other critical areas. This suggests that acute episodes which lead to anginal pain, coronary infarcts, little strokes, and death may require the conjunction of this slow deposition and consequent narrowing of the lumen with a superimposed and markedly increased coagulability of the blood. Such an increased coagulability has been shown to result from the heavy intake of fat in a single meal by normal persons. It may also be caused by an accelerated mobilization of lipids from depots to meet emergency energy demands in physical or psychic stress episodes. The nature of the ingested and deposited fat may thus be a significant factor in the blood stability and coagulability, normally and in episodes.

A study of the recalcification times of pooled citrated human plasmas has been made without and with the additions of sodium soaps. Saturated fatty acids show a remarkably enhanced ability to accelerate plasma gel formation as their chain length increases; sodium stearate often gives gels in 10 to 20 per cent of the control time. In the same plasma the sodium soaps of oleic, linoleic, and linolenic acids all behave about the same, and show coagulant effects comparable to those of lauric (C_{12}) instead of stearic (C_{18}) acid. By similar procedures several individual citrated plasmas have been treated with sodium soaps of the mixed fatty acids separated from common food fats. The average coagulation index values for one series of plasmas fell into the following order: corn oil, −5; safflower oil, −6; coconut oil, −9; oleic acid, −9; animal fat, −21, and stearic acid, −95. These plasma gel effects emphasize the importance of the blood coagulability and of the role of food fats in both the slow deposition and the catas

trophic incidents of arteriosclerosis and coronary deaths.

51. Studies Indicating Inactivation of Post-Heparin or Endogenous Plasma Lipoprotein Lipase during Triglyceride Lipolysis

H. Engelberg. From the Cedars of Lebanon Hospital, Los Angeles, Calif.

Evidence has been obtained in previous studies which suggested that post-heparin or endogenous lipemia clearing factor (lipoprotein lipase) was itself inactivated or altered during the process of lipolysis. To further investigate this question 3 sources of lipoprotein lipase were used: 1, fasting post-heparin plasma; 2, the citrate eluate of the $Ca_3(PO_4)_2$ adsorbate of post-heparin plasma; 3, fasting plasma containing endogenous lipemia clearing activity. In 8 experiments aliquots of plasma or of citrate eluate were placed in 2 tubes which were then incubated at 37 C. for 2 hours. Low-density human lipoproteins were added in excess to tube no. 1 at the start of the first and second hours, and to tube no. 2 only at the start of the second hour. Albumin was added as fatty acid acceptor in the experiments using citrate eluate; aliquots were removed from each tube every 15 min. for glycerol determination.

The results showed no or very little glycerol release during the second hour in tube no. 1. In tube no. 2 lipolysis during the second hour of incubation proceeded essentially at the same rate as in tube no. 1 during the first hour. These results substantiate that lipoprotein lipase is inactivated during lipolysis, a rather atypical property of an enzyme. Thus the failure to demonstrate lipolytic activity in the plasma of most individuals is not a valid objection to the accumulating evidence that indicates its normal role in lipemia clearing.

In other experiments evidence suggesting that heparin is a component of lipoprotein lipase was obtained.

52. Diet and Atherosclerosis, Additional Clinical and Laboratory Observations

P. F. Flynn, S. Splitter, H. Balch, A. Barcellini and L. W. Kinsell. From the Institute for Metabolic Research Highland-Alameda County Hospital Oakland, Calif.

Persons with manifestations of arteriosclerosis and/or hyperlipemia have been studied by means of history, physical examination, and laboratory examination.

Cardiac status has been evaluated with reference to electrocardiography, ballistocardiography, and in some cases exercise tests.

Peripheral circulation has been evaluated by the following means: inspection of extremities, palpation of the peripheral pulses, oscillometry, claudication time under controlled and semicontrolled conditions, pallor of elevated extremities, development of rubor on dependence, venous filling time and flush reaction and its time of appearance. Femorals and abdominal vessels were evaluated as to the presence of bruits.

Prior to institution of diet therapy at least 2 fasting bloods were drawn. On these cholesterol and plasma total lipids were determined, and in some instances fatty acid composition of lipid fraction was also determined.

Depending on the level of plasma lipids and clinical status, one of 3 diets was selected. Each of these diets contained more than 50 Gm. linoleic acid, but they differed in regard to the amount of saturated fat and carbohydrate. Those who failed to respond to the group 1 diet which contained no animal fat were placed on formula diets containing large amounts of safflower oil or ethyl linoleate.

Subjective and objective improvement occurred in some of the patients having peripheral arteriosclerosis. None of the postcoronary patients with angina pectoris has had significant relief of distress.

Clinical and laboratory findings will be presented and critically evaluated.

53. In Vitro Studies of Lipids in the Human Aorta Using a Double-Chambered Diffusion Apparatus

William C. Foster. From the Laboratory of Physiology Research, Misericordia Hospital, Philadephia, Pa.

The double-chambered diffusion apparatus of Delrue has been modified for the purpose of studying physical and chemical properties of the human aorta in vitro. Discs of tissue, about 2.5 cm. in diameter, are cut out at autopsy from the thoracic and abdominal aortas, stretched between the 2 ground-glass orifices of the diffusion chambers, and fixed into position by a patented pinch clamp. The chambers are then filled with lactated Ringer's solution. The left chamber, exposing the lumen side of the aorta, is pressurized to 100 mm. Hg through a connection with an aspirator bottle of solution placed 136 cm. above the apparatus. The experiments are conducted at 38C. with a mixture of 95 per cent oxygen and 5 per cent carbon dioxide bubbling into the solution. Samples for analyses may be withdrawn from either chamber at any time during the experiment. C-14 cholesterol ester emulsions, added to the lactated Ringer's solution, are sampled half-hourly after exposure to aortic tissue for a period of 2 hours and the radioactivity is determined. Penetration studies of the aorta are made by stripping the

tissue and measuring the radioactivity. The advantages of this apparatus are: 1, only small amounts of isotopic material are necessary in this system, 2, control of the radioactive material, and 3, the use of human material.

54. Effects of Stilbesterol, Methyl Linoleate, Vanadium Sulfate and Chronic Starvation on Preestablished Cholesterol Atherosclerosis in the Rabbit

Nelly Gutmann-Auersperg, Donald Hospes and Paris Constantinides. Anatomy Department, University of British Columbia, Vancouver, B. C., Canada

One hundred and forty-four New Zealand White rabbits were placed on a high-cholesterol diet for 2 months. At the end of this period, 18 sets of 6 animals with nearly identical plasma cholesterol curves were selected and arranged in 6 groups of 18 rabbits (each group with a nearly identical population of lipemic response patterns), while the remaining 36 rabbits were discarded. One group was killed immediately, but the other 5 switched to normal diet for another 2 months before being killed. Of the latter 5 groups, 1 remained untreated (to demonstrate the progress of atherosclerosis despite dietary cholesterol withdrawal) whereas the other 4 were treated with stilbestrol, methyl linoleate, vanadium sulfate and chronic starvation, respectively.

Atherosclerosis was assessed separately in the upper and lower aorta of each rabbit by the following battery of criteria: 1, total area of lesions; 2, cholesterol and total lipid content of lesions; 3, thickness of the thickest plaque; 4, detailed histological pattern of standard lesions (8 parameters in frozen and paraffin sections).

While none of the treatments accelerated the slow decline of hypercholesterolemia that follows dietary cholesterol withdrawal, stilbestrol exerted a very pronounced arresting effect on the progress of atherosclerosis in both the upper and the lower aorta and it tended to change the histological pattern of the pre-established lower aortic plaques in a direction suggesting stimulation of scavenger cell activity; methyl linoleate exhibited a moderate arresting action on the progress of the lower (younger) aortic lesions only; vanadium sulfate did not affect continued atherogenesis under the present conditions and chronic starvation tended to increase it by some criteria.

The direct or indirect nature of the atherostatic action of stilbestrol as well as the partially favorable results with linoleate merit further investigation.

55. Serum Cholesterol and Beta Lipoprotein Levels in Matched White, Non-White, Maternal and Prepubertal School Children

Curtis G. Hames, Claxton, Ga.

Evans County, Georgia, has a stable homogeneous population of 4,000 white persons and 2,400 Negroes. It is a rural nonindustrialized southern community.

The investigator was born and practices in the study county.

The α/β-lipoprotein ratios were determined by electrophoretic separation of the serum and staining with Oil red O according to a modification of the method of Jencks, Durrum, et al. Cholesterol determinations were carried out by a modification of the Zlatkis, Zak and Boyle method. Random crosschecks by the Schoenheimer-Sperry method were found to be in satisfactory agreement.

There are 191 matched mother's and fetal-cord blood from all births in the county. Blood samples were obtained from all self deliveries plus those submitted by cooperating midwives and physicians. School-children data were obtained from a blood typing program in the first 3 grades of the 2 county schools. There were 421 school children.

Results. 1. Fetal cholesterol and β-lipoprotein levels were not significantly different among race-sex groups. 2. Both measures were significantly higher ($p = 5$ per cent) among white than Negro mothers, especially mother's cholesterol levels for those having female infants. 3. In β-lipoproteins there was no correlation between the levels of mother and infant. There was also no association between mother's cholesterol and fetal cholesterol except for white male children, where the correlation coefficient ($r = 0.29$) was highly significant ($p = 1$ per cent). 4. White school children's cholesterols were approximately 9 mg. per cent higher ($p = 1$ per cent) than the Negro, and the β-lipoproteins were about 4 per cent higher. Sex among the school children had no effect on both measures, except that white males were 2 per cent *lower* than white females in β-lipoproteins. 5. Additional correlations are being performed with blood type, height and weight of the school children.

The implications of these data in relation to mortality differentials will be discussed.

56. The Relationship between the Intensity of Anthrone Color and the Biological Activity of Sodium Heparinate

J. R. Helbert and K. D. Brown. From the Department of Biochemistry, Marquette University School of Medicine, Milwaukee, Wis. and Veterans Administration Hospital, Downey, Ill.

Most carbohydrates react with anthrone in strong sulfuric acid to give a blue-green color with maximum absorbency at 620 to 625 mμ. (Annal. Chem. **24**: 1,576, 1952; Ibid., **25**: 1,656, 1953; Ibid., **27**: 1,791, 1955). However, under other conditions (Annal. Chem. **28**: 1,098, 1956) we have

found that uronic acids react with anthrone to yield a red color with maximum absorbency at 540 mμ.

Sodium heparinate also reacts with anthrone to yield a red color with maximum absorbency in excellent agreement with that of monoglucuronic acid. Also, the absorbency concentration relationship conforms to Beer's law, at least up to concentrations of 100 μg./6 ml. The absorbency of glucosamine hydrochloride, after reaction with anthrone, has been determined to be zero; and the absorbency concentration plot of 1:1 mixtures of glucuronic acid and glucosamine hydrochloride, after reaction with anthrone, is congruent with that of glucuronic acid alone. Therefore, it appears that color produced by sodium heparinate with anthrone is caused primarily by the glucuronic acid present in the polymer.

However, the amount of color obtained with sodium heparinate is about 4 times greater than that anticipated from the amount of glucuronic acid estimated to be present on the basis of the repeating unit proposed by Wolfrom (J. Amer. Chem. Soc. **72**: 5,796, 1950.) The reason for the unusual behavior of sodium heparinate is unknown, but is currently under investigation in this laboratory.

The relationship between the intensity of anthrone color and the biological activity of a series of sodium heparinates has been examined. These heparinates were from several sources and had biological activities ranging from about 30 to 150 USP units/mg. The absorbency of the anthrone color increases directly as the biological activity, although the relationship is not a straight-line function. The preliminary evidence suggests that it may be feasible to use some form of the anthrone test to assay heparin.

57. Effects of Hyperlipemia on Rabbit Intraocular Atheromatous Aortic Homotransplants

A. C. Higginbotham and Frances H. Higginbotham. From the Department of Microanatomy and Organology, West Virginia University School of Medicine, Morgantown, W. Va.

Hyperlipemia is accompanied by decreased arterial oxygen saturation (Kuo and Whereat, Circulation **16**: 493, 1957) and by increased erythrocyte agglutination, altered blood flow and vessel pathology in experimental animals and man (Cullen and Swank, Circulation **9**: 335, 1954; Higginbotham et al., Anat. Rec. **122**: 459, 1955; Higginbotham and Williams, J. South Carolina M.A. 53: 1, 1957. Myasnikov (Circulation **17**: 99, 1958) reported greatly increased aortic atherosclerosis in hypoxic cholesterol-fed rabbits.

The effects on pre-established atheromatous lesions of hyperlipemia and its concomitant metabolic and circulatory disturbances were studied in 2 experimental groups of rabbits by the use of the intraocular homotransplantation technic introduced by the author (Science **125**: 554, 1957). The sequential histochemic changes occurring in such transplants during spontaneous regression in healthy hosts have been described (Arch. Path. In press).

Normal and atheromatous aortic homotransplants were made in rabbits on normal diets. Lipotrophic extract (Wyeth) was given intravenously (5 mg. week) from 22 to 42 days. Moderate to extensive necrosis of the plaque occurred in several transplants. Medial necrosis with fat deposition occurred in the normal transplant. Some cholesterol clefts were present in the oldest transplants, but since no decrease in sudanophilia was observed other body fat probably contributed to the hyperlipemia.

Similar homotransplants were made in rabbits fed oil-enriched diets for 39 to 276 days. Necrosis and calcification occurred in some atheromatous transplants. Small monorefringent lipid deposits occurred in the normal transplants, and one transplant had extensive medial cartilaginous metaplasia. Although numerous cholesterol clefts were present in the oldest atheromatous transplant, regressive processes appeared to have been retarded.

Results obtained suggest that hyperlipemia with associated hypoxia is not only atherogenic but retards regression and promotes necrosis and calcification of existing lesions. This supports the rationale for low-fat diets in clinical atherosclerosis.

58. Essential Hyperlipemia: Incidence and Therapy

Kurt Hirschhorn, Rochelle Hirschhorn, Marco Fraccaro and Jan A. Böök. From the Department of Medicine, New York University Post-Graduate Medical School, New York, N. Y., and the State Institute for Human Genetics, Uppsala, Sweden.

Essential hyperlipemia is an inherited disease that is thought to be due to a defect in the lipemia clearing system. The abnormal gene manifests itself by a delay in clearing from the plasma of ingested fat, milky serum with elevation of all lipids but mainly of the neutral fats and the appearance of severe arteriosclerosis in early adulthood. A double dose of the gene produces hepatosplenomegaly, abdominal crises, milky serum and childhood arteriosclerosis, and it usually causes death before the reproductive age.

Random nonfasting blood samples were obtained from 998 consecutive new students at the University of Uppsala in Sweden. Plasma optical density was measured. The 275 students, whose optical density readings were higher than the lowest value associated with visual opalescence, were

recalled for fasting specimens. Two hundred and seventy of these returned and were examined for serum optical density and for total lipids by the method of Kunkel et al. Those students whose serum showed an optical density of over 80 or showed total lipids of over 800 mg. per cent or were borderline in both catagories were recalled for a fat-tolerance test.

The 36 students in this group, as well as 5 randomly chosen controls and 2 healthy staff members, had a complete medical history, physical examination, urinalysis for sugar and protein and a 9 hour fat-tolerance test with a 90 gr. fat load, as well as serum total cholesterol determination. Sixteen of these students demonstrated marked delay in clearing of ingested fat, while 4 were borderline. Because of the inability to perform fat-tolerance tests on all 998 students it is felt that at least 10 more students would have fallen into the category of essential hyperlipemia, giving a total estimated incidence of 3 per cent. This is based upon an analysis of duplicate fasting samples in those students who were recalled.

Ten of the hyperlipemic students were placed on the spaced fat-feeding régime of Wilkinson. This resulted in a highly significant decrease in optical density of the serum as well as in serum cholesterol in all of the students on the régime.

59. Decreased Aortic Atherosclerosis in Fibrocystic Disease of the Pancreas

Russell L. Holman. From the Department of Pathology, Louisiana State University School of Medicine, New Orleans, La.

Fibrocystic disease of the pancreas is a disease of theories. It is not the purpose of this presentation to compound these theories, but rather to report a simple observation that may be related to the disturbed lipid metabolism of this disease and that of another poorly understood entity, namely atherosclerosis.

The degree of fatty streaking of the aorta (percentage of the intimal surface that stains red with Sudan IV) in 18 cases of fibrocystic disease of the pancreas was compared with that in 21 control cases of the same age group (6 to 13 years, inclusive). All cases were in the white race. Whereas the average for the control group was 4.1 per cent of the intimal surface involved with fatty streaks, that for the fibrocystic group was less than 1 per cent; and this latter group included one male aged 7 years whose aorta was entirely negative.

Data are presented which argue against the obvious explanations (1, decreased absorption of fat and 2, extensive terminal infections such as bronchiectasis) and which support the possibility that an increase of serum lipase produced by pancreatic duct obstruction prevents the accumulation of lipids that constitutes the first stage of atherosclerosis.

Regardless of the ultimate interpretation of these data, fibrocystic disease of the pancreas appears to be the first documented human disease with *decreased* atherosclerosis.

60. Changes in Serum Lipids and Coagulogram in Man with Prolonged Administration of Sodium Polyethylene Sulfonate

Peter T. Kuo and Harold Wurzel. From the Hospital of University of Pennsylvania, Philadelphia, Pa.

The polymerized sodium salt of ethylenesulfonic acid (U-6812) has been shown to possess heparin-like activities. The drug was administered intramuscularly or subcutaneously to 12 postmyocardial infarction patients in doses of 30 to 60 mg./day for periods of 3 to 13 months. Serum cholesterol, phospholipids, total esterified fatty acids and electrophoretically separated lipoprotein fractions were determined and a blood coagulogram taken at 1 to 3 week intervals in each patient before and during drug administration. A significant increase in the serum α-lipoproteins and a decrease in the β-fraction were observed in 11 of the 12 patients after 2 weeks of U-6812 injections. This change in serum lipoprotein pattern became maximal in about 4 weeks and it was maintained with continual drug administration. U-6812 failed to alter the serum lipoprotein pattern of one patient who has an unusually high α-fraction. The mean serum phospholipid levels tended to increase in the majority of patients receiving U-6812 therapy. Their serum cholesterol and total esterified fatty-acids levels were not significantly altered. At one time or another, 3 out of 7 patients showed a reduced amount of the labile factor and prothrombin concentration, 5 showed a poor consumption of prothrombin, 4 a fall in platelet count, 3 an increase in sensitivity to heparin and 4 a suboptimal yield of thromboplastin (either serum or alumina plasma) in the thromboplastin generation test. However, the clotting time and clot retraction of all patients were normal. None of the treated patients developed hepatic dysfunction, alopecia, bone decalcification, feminization or hemorrhagic complication during the period of observation.

61. Further Investigations on the Importance of Parathyroid and Adrenal Cortical Hormones in Cardiovascular Necrosis

David Lehr, Marilyn Krukowski and Onita Ricard. From the Department of Physiology and Pharmacology, New York Medical College, Flower and Fifth Avenue Hospitals, New York City, N. Y.

Albino rats survived bilateral nephrectomy without therapy usually for 3 to 4 days. The majority of such animals manifested the typical picture of extensive cardiovascular and smooth-muscle necrosis previously obtained with standard renal injury (Lehr, et al., Bull. New York M. Coll. **15**: 130, 1952). Administration of parathyroid extract on the first and second day after nephrectomy resulted in dramatic enchancement of the incidence and especially in the severity of these lesions. A similar aggravating effect was achieved in nephrectomized as well as nephrectomized-adrenalectomized rats by injection of DCA and/or cortisone. On the other hand, rats deprived of their parathyroid glands prior to nephrectomy failed to develop any muscular necrosis even in the presence of excessive amounts of glucocorticoids and mineralocorticoids.

In a further exploration of adrenal cortex-parathyroid "synergism," it was found in parathyroprival rats that after simultaneous adrenalectomy-nephrectomy the administration of exogenous parathyroid hormone still produced typical muscular necrosis. However, under these conditions exogenous adrenal corticoids did not increase the muscular injury. These facts deny a peripheral synergistic action of the hormones from the parathyroid and adrenal cortex.

Results of experiments in rats that were adrenalectomized 10 days prior to nephrectomy and maintained on large daily dosages of cortisone and/or DCA indicated that in the presence of intact parathyroid glands either of these hormones as well as their combination permitted the emergence of typical muscular necrosis.

The relationship of adrenal cortical hormones to the parathyroid gland, as is apparent from the findings in both renogenic and reniprival cardiovascular and smooth-muscle injury, is believed to be consistent with the concept of an adrenal cortex parathyroid "axis."

62. Readily Extractable Cholesterol: A New Method for Investigating the Lipid Binding Ability of Human Blood Serum

Martin Marcus and Daniel A. Sherber.. From the Metabolic Research Laboratory, Fordham Hospital, New York, N. Y.

In a search for new and easily performed laboratory tests which might be of value in clinical atherosclerosis research, the method of Byers et al. for readily extractable cholesterol (REC) seemed of probable importance. Accordingly, a study of the usefulness of this method, its validity and its clinical applications was undertaken.

In order to achieve reproducibility, several modifications of the Byers method were introduced. These included the use of glass extraction tubes of precision design, close attention to temperature and reagent purity, particularly with respect to ether which must be peroxide-free.

Studies were made of normal persons, patients with atherosclerosis, and young persons with hypercholesterolemia but no other evidence of disease.

It was found that in hypercholesterolemia the REC was greater but the increase over normal was not proportional to the total cholesterol nor to the total lipid increase which were greater.

Efforts to determine the origin of the REC proved that both α-lipoprotein and β-lipoprotein contributed a proportional share. Patients with electrophoretically demonstrated, increased β-lipoprotein did not show any higher REC than normal persons. Electrophoresis also revealed that all the cholesterol is separated from its protein bonds by the method. Thus it is evident that some other factor, unknown at this writing, prevents the migration of lipid from water to ether phase. Since adrenalectomy, Addison's disease, and adrenal insufficiency have been shown to be accompanied by a profound increase in REC, the existence of a "lipid-binding factor" is postulated. This may be of adrenal origin or under adrenal influence.

63. Normal Standards of Height and Weight for Ages 65-94

A. M. Master, R. P. Lasser and Gloria Beckman New York, N. Y.

In 1955 more than 14,000,000 Americans were 65 years of age or older, and in 1975 this figure will probably be at least 20,500,000.

A standard table of normal weight per/in. of height has been constructed for men and women of from 65 through 94 years of age. The table includes both mean weight per/in. of height and a variation $\pm$ 10 per cent and $\pm$ 20 per cent from the mean. This is the first study based upon a sample of sufficient size and adequate cross section of apparently healthy, ambulatory, over 65-year white population which may be used as a standard of reference. No subjects with cardiovascular renal disease nor any living in institutions were used. Total sample was 2,925 males and 2,694 females.

Mean weights were calculated and plotted for each inch of height. A smooth, curved line was drawn for 10 year age groups and each sex. Standard tables were then prepared from these curves. This procedure insured a more uniform relationship of weight and height than did crude data.

Ninety per cent of data was distributed between the following heights: males, 5 ft. 1 in. to 6 ft. 1 in., females, 4 ft. 10 in. to 5 ft. 8 in. These were the points which were considered valid in drawing

the line of best fit. Which limits about the mean weight per/in. of height that may be considered abnormal are still under consideration.

In both sexes and at all heights people became lighter with advancing age. Shorter people tended to lose more weight than taller ones and women more than men.

We have established a table of normal weight per/in. of height for men and women aged 65 to 94 years. The table may be used to study obesity and cardiovascular diseases and to relate weight to morbidity and mortality in general.

64. Effects of Estradiol in Rats with Altered Cholesterol and Phospholipid Metabolism

Merle S. Moskowitz, W. Norman Brand and Richard A. Rasmussen. From the Department of Pathology, University of Chicago School of Medicine, Chicago, Ill.

Certain effects of estrogens on serum lipids and coronary arteries in the rat have been reported previously from this laboratory. For a study of the mechanism of estrogen action, these and other effects have now been investigated under other conditions.

In the present studies, mature male rats fed an atherogenic diet by gastric tube received .033 mg. or .333 mg. estradiol (Progynon-B, Schering) daily for 8 weeks. Serum cholesterol and lipid phosphorus levels rose in both cases and reached their peak at 5 weeks. Although the rats receiving .333 mg. of estradiol showed a 40 per cent greater rise in cholesterol than those on the lower dose, serum cholesterol:lipid phosphorus ratios (C/P) remained higher in the rats receiving .033 mg., because of proportionately lesser hyperphospholipemic reponse. During this brief period there was no difference in incidence or degree of coronary sudanophilia between these 2 groups.

In order to study the influence of extreme alterations in cholesterol metabolism on the estrogen effect, hypercholesterolemia was induced by the *ad libitum* feeding, of a high-fat diet containing 2 per cent ox bile, to mature male rats. After 8 weeks the hypercholesterolemia was marked and the C/P was extremely elevated. Estradiol injections (.333 mg./day) were then initiated, and 3 weeks later the rats showed drastically reduced serum cholesterol levels and elevated lipid phophorus levels, resulting in depression of the C/P to almost normal values. Despite this improvement in the serum lipid pattern, the incidence of coronary sudanophilia at the end of 6 weeks of treatment was the same as in controls not receiving estradiol. Later, this trend was reversed.

In order to examine, also, the influence of disturbed phospholipid metabolism on the estrogen effect, the force-fed atherogenic diet was supplemented with diethanolamine (100 to 400 mg./Kg./day). Under these conditions the usual dietary hypercholesterolemia was somewhat suppressed, and with daily injections of estradiol (.333 mg.) marked hypocholesterolemic responses were observed in less than 2 weeks. The occurrence of coronary sudanophilia was apparently unrelated to the level of serum cholesterol; coronary lesions were observed in animals with serum cholesterol as low as 22 mg. per cent and with C/P less than half the average control value.

65. Plasma Unesterified Fatty Acid and Lipid Levels in Neoplastic Disease

Peter S. Mueller and Donald M. Watkin. From the General Medicine Branch, National Cancer Institute, National Institutes of Health, Bethesda, Md.

Forty-three patients with either solid tumor or leukemia and 8 patients with myeloid metaplasia, polycythemia vera, or Waldenström's macroglobulinemia were studied by serial determinations of fasting unesterified fatty-acid levels during the course of their disease. The unesterified fatty-acid levels were determined by isooctane extraction. Normal levels of unesterified fatty acid ranged from 0.100 to 0.700 mEq./1. and elevated values ranged form 0.700 to over 1.5 mEq./1.

A total of 126 determinations was done on the leukemia or solid-tumor patients, and 34 marked elevations were found. These elevations were correlated with clinical and laboratory evidence of active neoplastic disease. Remission of disease produced by a variety of chemotherapeutic agents resulted in a prompt return of the unesterified fatty-acid level to the normal range.

Every determination of plasma unesterified fatty-acid level in 4 patients with myeloid metaplasia, 3 patients with polycythemia vera, and one patient with Waldenström's macroglobulinemia fell well within the normal range despite evidence of active disease, such as rapid weight loss, anemia, or elevated white blood counts. Chemotherapeutic or isotopic treatment of disease in these patients produced no change in unesterified fatty-acid levels.

A limited number of triglyceride, phospholipid, and total lipid determinations has been done to date in the solid tumor and leukemia patients; marked elevation (188-1094 mg. per cent) of triglyceride levels were noted in 6 out of 9 determinations. These elevations were noted in very active disease and were always correlated with elevated plasma unesterified fatty-acid levels.

Three patients with solid tumor were studied during periods of consecutive daily infusions of fat emulsion for plasma lipid and unesterified fatty-

acid levels. Triglyceride levels from 1,560 to 3,482 mg. per cent and plasma unesterified fatty-acid levels from 0.630 to 1.3 mEq./l. were noted.

These data suggest that the plasma unesterified fatty-acid level rises with activity of neoplastic disease. Polycythemia vera and agnogenic myeloid metaplasia seem to be exceptions despite disease activity.

66. The Relationship between Bile Acid Secretion and the Dynamic Equilibrium of Cholesterol in Vivo

T. Nishida, A. Ueno and F. A. Kummerow. From the Department of Food Technology, University of Illinois, Urbana, Ill.

Day-old chicks were kept on a grain-type poultry ration for a 5-week period and then divided into 4 groups of 5 birds each. The hepatic ducts of the birds in group one and the hepatic and cystic ducts of those in group two were cannulated. The hepatic and cystic ducts of those in group 3 were ligated and the birds in group 4 served as normal controls. The birds were killed via heart puncture after a 6-day experimental period, the livers were removed and the serum cholesterol, liver cholesterol, serum lipoprotein and the amount and composition of the bile acids were determined. The results indicated that an increase in bile flow reduced serum cholesterol and lipoprotein levels and the inhibition of bile flow increased serum cholesterol and lipoprotein levels significantly. In the latter case the lipoprotein pattern became more heterogeneous with a significant increase of the lipoproteins in the low S_f range.

The level of dietary protein influenced the rate at which cholesterol-4-C^{14} was excreted. The bile collected from birds which had been kept on a high-protein synthetic diet for 5 weeks and injected with emulsified cholesterol-4-C^{14} excreted the labeled cholesterol as bile acids at a faster rate than birds on a low-protein diet. A dietary source of cholesterol depressed the excretion of bile acids-1-C^{14} but did not alter the ratio of excretion in birds kept on a high-protein diet as compared with those kept on a low protein diet. However, the rate of incorporation of acetate-1-C^{14} into liver cholesterol was not altered significantly on a high-protein diet.

67. Affinity between Fibrin and Fat: Proposed Synergistic Relation in Atherosclerosis According to the Thrombolipid Theory

Robert M. O'Neal, Wilbur A. Thomas and W. Stanley Hartroft. From the Department of Pathology, Washington University, St. Louis, Mo.

Of various hypotheses concerning the pathogenesis of atherosclerosis, 2 opposing theories presently prevail. One theory holds that arterial plaque formation is initiated by deposition of lipid, and the other holds that it is initiated by deposition of fibrin. Our observations suggest a third theory that is in accord with most or all established facts presented by both "lipid" and "thrombotic" schools. Arterial plaques may well be the result of deposition of a combination of lipids and thrombi ("thrombolipid theory"). Some evidence in support of this thrombolipid theory has been obtained by a study of thrombolism in rabbits. According to results of experiments undertaken in this laboratory, strong affinity exists between thrombi and lipids; blood lipids rapidly enter thromboemboli; fat remains through their progression from thrombi to completely organized fibrous intimal lesions characteristic of arteriosclerosis.

The purpose of the present experiment was to determine the relationship between dietary fat and the fat found in pulmonary thromboemboli in rabbits. Sixty-nine rabbits survived for 5 weeks, but many others died. All received 10 ml. of clot-suspension/week intravenously, and various fats were given by gastric tube. Small amounts of lipid were demonstrable in pulmonary arterial thromboemboli of all rabbits, but in rabbits fed large amounts of fat the quantity of fat in thrombi, as seen in tissue sections, was sometimes dramatically abundant. Since the clots were originally formed in vitro, and at that time did not contain appreciable amounts of fat, lipid must have entered them after they had lodged in pulmonary arteries. These observation indicate selective affinity of fibrin for fat. Mural thrombosis favors lipid deposition; lipemia and mural lipoidosis favor thrombosis. The presence of fat in thromboembolic-induced lesions at all stages of organization is evidence that atherosclerotic lesion containing fat and fibrous tissue could well result from organization of fatty mural thrombi.

68. Serum Lipoprotein Cholesterol: Factors Associated with Alteration of the Beta Fraction

Harold H. Orvis, Richard C. Fowler, Isa A. Fawal and John M. Evans. From the Department of Medicine, The George Washington University School of Medicine, Washington, D. C.

The amount of serum cholesterol in the α- or β-lipoprotein fraction is determinable after separation by paper electrophoresis (Langan et al.). This approach has been used to evaluate therapy employed to reduce β-lipoprotein and the ratio of β- to α-lipoprotein. It seemed pertinent to review our 2 year experience with these determinations with particular attention to factors or disorders associated with an abnormal β-fraction.

Elevation of the percentage of cholesterol in the β-lipoprotein fraction (PBC) has been observed in patients with coronary disease, xanthomatosis, hyperlipemia states, nephrosis, hepatobiliary disease and pancreatitis. In serial observations, increasing PBC was seen in patients receiving intravenous fat emulsion (Lipomul), in chlorpromazine jaundice and in acute pancreatitis. It is noteworthy that total serum cholesterol, generally elevated when PBC is increased, was usually normal in patients with pancreatitis.

Decreasing PBC, approaching the normal range, was demonstrated in nephrotics under steroid therapy and in a patient given a corn oil diet. The PBC fell to less than normal in 2 pancreatectomized subjects and in a patient with carbon tetrachloride hepatitis.

PBC was not altered by drug therapy of hypertension, administration of a choleretic (Gallogen, 1.5 Gm./day) or pyridoxine (300 mg./day), or in subjects in whom total cholesterol was reduced by an unsaturated dietary fat supplement. We have evaluated 14 normal males, aged 20 to 30, eating a low-fat, low-protein diet for periods of 2 to 9 years. The lipoproteins were practically identical with those obtained from matched control subjects. It is of interest that the PBC in controls is relatively constant when sampled biweekly for many months.

Comment: In this study the majority of subjects with markedly altered β-lipoprotein had pancreatic or hepatobiliary disease, with the exception of those with hyperlipemia. It is apparent that total serum cholesterol may be reduced without altering the percentage distribution of lipoprotein cholesterol and conversely, a shift in lipoprotein cholesterol distribution may occur without significant changes in the total cholesterol.

69. Evidence for Antithrombin Functioning as a Lipoprotein Lipase (LPL) Co-factor

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Recent reports from our laboratory have indicated that lipoprotein lipase (LPL) co-factor is deficient in arteriosclerotic subjects and that thrombin inhibits the LPL system (J. Appl. Physiol. **11**: 450, 1957; J. Gerontol. **13**: 32, 1958; Circulation **14**: 502, 1956) .

It is our purpose at this time to report on experiments which indicate a mutual identity between LPL co-factor and a serum antithrombin. LPL system activity was measured spectrophotometrically by incubating increasing quantities of LPL or serum (as source of co-factor) with 1 per cent sesame oil as substrate in the presence of thrombin. Incubations were performed at 37C. in a shaking bath. The volume of eacl. tube was brought to 1 ml. with 1:1 Sodium chloride-phosphate buffer (pH 7.2, T/2 = 0.1). Sufficient thrombin, 80 units or more, was used to exert a significant inhibition of the LPL system. It was found that increasing the concentration of LPL was relatively ineffective in removing thrombin inhibition, whereas increasing serum always removed the inhibition. This indicated that the site of thrombin inhibition in the LPL system was a serum factor.

Clotting time experiments were conducted where thrombin activity was measured after incubation of 20 units of thrombin for varying periods of time with buffer, 0.15 ml. serum, 0.1 ml. sesame oil, and increasing quantities of LPL (1 to 7.5 mg.). It was found that LPL decreases the clotting time of the serum. As the concentration of LPL increases, the clotting time decreases.

It would appear from this data that LPL employs a serum antithrombin as a co-factor. However, until more direct chemical and physical evidence is available, it is not warranted to assume that the arteriosclerosis co-factor deficiency also represents an antithrombin deficiency.

70. A Correlation of Serum Lipids, Lipoproteins, and Blood Sugar Levels in Diabetes Mellitus

Julius Pomeranze, Harold Feldman, Edward J. King, Ralph J. Lucariello, and Julius Simon, New York, N. Y.

One hundred and four patients of all ages and with diabetes in varying degrees of severity were observed for serum lipid, electrophoretic lipoprotein analysis and blood sugar levels. These patients were unselected and were included whether diabetic control was good or poor. In those poorly controlled, attempt at good control was made and the serum was then observed under these changed conditions. In some well controlled patients, control was permitted to deteriorate and the patients were then restudied. In some instances, repeated analyses were made without regard to the diabetic status. On most patients, urea nitrogen determinations were also made. Serum was always drawn in the fasting state.

Clinical diabetes mellitus, unlike that in the depancreatized animal is not a simple or standard state. In human beings it is associated with many other abnormalities, deficiencies, diseases and disorders. Correlative data is therefore difficult to assess in this complicated condition. Biochemical data can be significantly altered by age, sex, weight, state of nutrition, degree of degenerative

hange, renal and hepatic function, and cardiac tatus, in addition to other factors.

Nevertheless, certain significant results were seen this evaluation study. 1. β-lipoprotein, choles- rol and total lipid levels are significantly higher the older diabetic patient, despite the increased verity of the disease in younger patients. 2. here appears to be some degree of correlation etween elevated blood sugar levels and β-lipo- rotein and total cholesterol levels. 3. Improve- ent in diabetic control, within certain limits, reates more normal levels of total lipids, choles- rol and β-lipoproteins.

71. The Effect of Feeding Butter and Margarine on the Development of Atherosclerosis in Swine

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The in vivo activity of clotting is increased during alimentary lipemia in subjects with atherosclerosis. The increased activity is greater after meals of butter than of margarine. This evidence suggests that if increased activity of the coagulation mechanism is a factor in the development of atherosclerosis, the feeding of butter to animals should have a more marked effect than would margarine.

Thirty-three swine matched for age, sex, weight, breed and nature of their coagulation mechanism were divided into 3 groups. Animals in group A received cereal mash and butter to 40 per cent of their calories, group B received cereal mash and margarine to 40 per cent of their calories, and group C cereal mash. After 3 to 8 months' feeding the animals were killed and studied.

Atheromatous plaques were most numerous in the vessels of the butter-fed swine. After 3 months, the lesions were most marked in the ascending arch of the thoracic aorta, but later more marked in the abdominal aorta. The plaques were intimal thickenings composed of fibrous tissue, a hyaline-like material and lipid. They resembled the lesions seen in human atherosclerosis, rather than those found in rabbit atherosclerosis.

Although the feeding of butter to swine caused a more rapid development of atherosclerosis than the feeding of margarine, there was no associated elevation of the blood cholesterol and phospholipid levels. The butter-fed animals had evidence of a more active clotting system. This suggests that butter contains material which accelerates the development of atherosclerosis in swine and also increases the activity of the clotting system.

72. Neural Regulation of Human Blood Cholesterol Levels

Daniel A. Sherber and Martin Marcus. From the Metabolic Research Laboratory, Fordham Hospital, New York, N. Y.

The suggestion of Miasnikow that blood lipid levels are under central nervous system control in rabbits, and the recent demonstrations of stress and emotional crisis effects on blood lipid levels by Rosenman et al. as well as the findings by Sherber and Marcus, reported at these meetings last year, on physical stress effects on blood lipids, prompted a further investigation into the neural contribution which may be a part of the stress phenomenon.

Nervous system effects were shown in 2 ways: by extremely rapid changes in serum cholesterol levels which could only be attributed to a neural mechanism, and by the effect of different groups of drugs which have central nervous system action. These groups were characterized by phenobarbital, promazine hydrochloride and meprobamate.

An extremely rapid serum cholesterol response was noted in a group of patients after the ingestion of 400 ml. of water. Blood was drawn at 1-min. intervals for at least 15 min. before and 15 min. after drinking. Within 5 min. after water ingestion, the level had decreased as much as 19 per cent, averaging 15 per cent for the group. Response had already begun after 1 minute. Fifty per cent of the patients studied showed this effect.

Studies with the drugs described above revealed that only promazine hydrochloride had any effect on blood cholesterol. Following administration of 100 mg./day for 3 days, the level had dropped between 11 and 19 per cent. During the periods in which phenobarbital or meprobamate or placebo for promazine hydrochloride was given, serum cholesterol returned to pretreatment levels. The significance of these findings will be reported.

73. Unesterified Fatty Acid and Triglyceride Changes in the Blood and Lymph after Chyle-Infusion

John J. Spitzer and Paul S. Roheim. From the Department of Physiology, Hahnemann Medical College, Philadelphia, Pa.

I^{131} labeled triolein was fed to dogs. Chyle (about 100 ml.) taken from these donor animals was infused into normal fasting dogs under anesthesia. Simultaneous blood samples were obtained from the femoral artery, femoral vein, portal vein and hepatic vein of the recipient animals.

Unesterified fatty acids (UFA), triglycerides and radioactivity were determined in all samples.

Before the infusion, femoral venous arterial differences in UFA were noted. These differences disappeared during the infusion and appeared again after the infusion. The liver removed UFA, while the abdominal region frequently liberated UFA both before and after chyle infusion. During infusion the leg removed triglycerides, as did the liver and the abdominal region. Radioactivity data were similar to the triglyceride findings.

In another group of experiments, the thoracic duct of the recipient dog was cannulated and lymph collected continuously. Chyle infusion in these thoracic-duct cannulated dogs caused similar arteriovenous changes in plasma UFA and triglyceride concentrations, as in the previous group. An increase in lymph flow and a delayed appearance of radioactivity in the lymph was also observed.

74. Experimental Renal Hyperlipemia

Judy A. Spitzer and John J. Spitzer. From the Department of Physiology, Hahnemann Medical College, Philadelphia, Pa.

The role of the kidneys in lipid transport was investigated in the course of studies on fat metabolism. Johnson, Bauer, Hirsch and Carbonaro (Arch. Path. 1951. **52**: 115) described lipemia in rabbits 1 to 3 days after unilateral occlusion of the renal vein or artery. In the experiments noted below, the blood chemical analyses were extended, ultracentrifugal patterns of plasma lipoproteins studied, and the findings supplemented by histologic tissue examinations.

The left renal artery or vein of rabbits was clamped for 20 minutes under nembutal anesthesia. The animals received penicillin injections repeatedly, following the operation. In control animals, the sham operation consisted of surgical exposure of the renal area for 20 minutes. Otherwise, they received treatment identical to that of the experimental animals.

Rabbits vary a great deal in their normal blood lipid level. In these experiments, the esterified fatty-acid and triglyceride levels increased in a majority of the operated animals. The plasma of experimental animals exhibited a substantial overall increase ultracentrifugally in all low-density lipoprotein classes studied ($S_{-1.21}$ 10-52, 52-74, 74-300, and 300-500). High-density lipoproteins ($S_{-1.21}$ 1-10 group) tended to decrease rather than increase after the clamping of the renal vessels. (These analyses were performed at the Division of Laboratories and Research, New York State Department of Health, Albany, N . Y.). Urine samples of a few postoperative lipemic animals were examined by ultracentrifugal flotation and by paper electrophoresis. No lipoproteins or signs of proteinuria were found by these technics. Yet the urine samples contained considerable amounts of esterified fatty acids. The results of nearly all blood-urea-nitrogen determinations fell within the normal range. Histologic examination of the operated kidneys showed no signs of glomerular damage but the kidneys exhibited tubular degeneration and in some cases necrosis.

75. Effects of Vitamin Deficiencies on Cholesterolemia and Atherogenesis in Cockerels on High Fat, High-Cholesterol Diets

Jeremiah Stamler, Ruth Pick and Louis N. Katz. From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

This series of 3 experiments was undertaken to assess the effects of vitamin deficiencies on cholesterolemia and atherogenesis in cockerels fed a high-fat, high-cholesterol diet. A purified ration was used throughout, supplemented with 1 to 2 per cent cholesterol +5 per cent cottonseed oil. Protein content was 36 per cent, 15 per cent and 20 per cent in the 3 series of experiments. Nine groups were studied: 1, all vitamins in adequate amounts; 2, diets deficient in A and D; 3, in K and E; 4, in biotin, inositol and PABA; 5, in B_6, B_{12} and folic acid; 6, in B_1, riboflavin, niacin and pantothenate; 7, in B_6; 8, in B_{12}; 9, in folic acid. With a high-protein diet (36 per cent), no effects of vitamin deficiency on cholesterolemia were noted. However, 2 groups (4 and 5) exhibited intensified coronary atherogenesis. With a low-protein diet (15 per cent), 3 groups (2, 4 and 5) exhibited intensified hypercholesterolemia. Preliminary data suggest that deficiency of a single vitamin (e.g. B_6 or B_{12} in groups 7 and 8) was also associated with intensified hypercholesterolemia. These findings indicate that in the genesis of hypercholesterolemia and atherosclerosis, nutritional-metabolic interrelationship exist between the vitamins and fats-cholesterol.

76. Studies on Rats With Dietary Induced Myocardial and Renal Infarcts

Wilbur A. Thomas, Robert M. O'Neal, and W. Stanley Hartroft. From the Department of Pathology, Washington University School of Medicine, St. Louis, Mo.

For half a century we have known how to produce a form of arteriosclerosis in animals by feeding cholesterol with and without adjunets such as thiouracil. But thrombotic complications occurred only rarely.

Last year we reported a dietary method of producing thromboses with myocardial and renal in-

farcts in significant numbers of several small groups of male, adolescent (100 Gm.) rats.

Since the original report we have repeated the experiment several times with several variations and are prepared to answer some of the questions that were raised by the original results. To date, 15 variations of the original infarct-producing diets have produced infarcts in 73 of 353 rats (21 per cent), many of which involved both the heart and the kidneys. Five other variations in 50 rats have not resulted in infarcts.

Incidence in the groups with infarcts has been variable, ranging from 20 per cent to 60 per cent in small groups. Because of this variability it has been necessary to use large numbers in making comparisons when various dietary constituents were altered, thereby making rapid progress difficult.

We have found that infarcts can be produced in mature as well as immature rats, females as well as males; that supplements of corn oil even at the 20 per cent level (added to 20 per cent butter or partially hydrogenated fats) do not offer complete protection against infarction; that exceedingly high levels of cholesterol in serum are not necessary, infarcts having been produced in rats with terminal levels as low as 142 mg. per cent. Details regarding these and other features will be presented.

77. Further Aspects of ACTH-Produced Arteriosclerosis in the Rat

Bernard C. Wexler and Benjamin F. Miller. From the May Institute for Medical Research of the Jewish Hospital and Medical Center of Cincinnati, and the Departments of Pathology and Medicine, University of Cincinnati College of Medicine, Cincinnati, O.

Last year we reported the production of "severe, explosive arteriosclerosis" when rats were injected with ACTH. These female breeder rats, approximately 1 year old, were fed a regular diet. They developed fulminating lesions, i.e., coronary and peripheral arterial sclerosis and aneurysms. Males of the same age developed other and marked degenerative lesions, but no arteriosclerosis. In both sexes, the blood pressure became elevated.

A striking variety of lesions has been observed. Many morphological variations were seen, as well as early and advanced stages of the arteriosclerotic process. In the coronary vessels there were found intimal and medial proliferation, that frequently led to occlusion. In other instances, these arteries showed intimal calcification and dilatation. The abdominal aorta displayed swelling of the intimal ground substance, endothelial thickening with or without swelling of the medial ground substance, and elastic-tissue degeneration. In the carotid vessels, all changes were observed, as well as more advanced changes evidenced by calcification, cartilaginous metaplasia and bone formation. The arch of the aorta also manifested these advanced lesions. In the mesenteric arteries the changes appeared to be limited to intimal calcification and elastosis. Frequent thromboses were noted in the lower abdominal and femoral vessels. The renal interlobular branches showed intimal foam cell proliferation; the main renal arteries displayed intimal calcification and medial hypertrophy.

All the intimal lesions from the various sites are relatively free of lipid; they appear to contain either fibrinous, hyalin or lipoproteinaceous materials.

78. The Roentgenogram Findings of the Abdominal Aorta in the Evaluation of Atherosclerosis

Joseph B. Wolffe, Jack Ruthberg and Edward Siegal. From the Valley Forge Heart Hospital Medical Center, Fairview Village, Pa., and Wolffe Clinic and Hospital, Philadelphia, Pa.

Experimentally induced atherogenesis as well as clinical experience shows that the abdominal aorta is most vulnerable to this disease. Recognizing this fact, we have examined routinely the abdominal aorta roentgenologically, using the Potter-Bucky grid technique. Because the lateral view of the aorta shows the condition so well, no contrast medium is necessary. The analysis of 100 cases shows that this roentgenological examination aids in differentiating atherosclerosis from medial calcification and hyperplastic arteriosclerosis, since the latter two do not affect the abdominal aorta. We shall correlate the clinical, physical, electrocardiographic and biochemical findings with the degree of involvement as shown in the lateral view of the abdominal aorta.

In coronary disease as a result of atherosclerosis the following percentage was found: 1+ atherosclerosis of the abdominal aorta, 10 per cent; 2+, 20 to 30 per cent; 3, 40 per cent; 4, 70 per cent. There is a high percentage of coronary disease clinically (70 per cent) with a 4+ finding of atherosclerosis of the aorta. The degree of changes in the abdominal aorta cannot be fully correlated with the extent of coronary involvement, but there are few cases of coronary involvement without some evidence of atherosclerotic changes in the abdominal aorta. The roentgenologic appearance of the abdominal aorta correlates closely with the extent of the disease found at postmortem examination. Three cases selected from the autopsy material show the close correlation between the findings at the autopsy table and the findings demonstrated with the lateral view of the aorta by the Potter-Bucky grid technic.

SPECIAL ANNOUNCEMENTS

AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

TWELFTH ANNUAL MEETING

Wed. Oct. 22	9:00-12 noon Work Shop & Meeting, Committee on Lesions, Marshall Room and Room 236, Hotel Whitcomb	Committee Lunch	2:00-4:30 p.m. Work Shop & Meeting, Committee on Lesions, Marshall Room and Room 236, Hotel Whitcomb	
Thurs. Oct. 23	9:00-12 noon Work Shop & Meeting, Committee on Lesions, Marshall Room and Room 236, Hotel Whitcomb	Committee Lunch	2:00-4:30 p.m. Work Shop & Meeting, Committee on Lesions, Marshall Room and Room 236, Hotel Whitcomb	6:00-9:00 p.m. Registration ASSA, Mezzanine, Hotel Whitcomb ASSA 1st Board Meeting Windsor Room, Hotel Whitcomb
Fri. Oct. 24	8:00 a.m.-5:00 p.m. Registration ASSA, Mezzanine, Hotel Whitcomb 9:00-12 noon AHA and ASSA Joint Symposium, Genetic Factors Civic Auditorium		2:00-4:30 p.m. ASSA 1st Scientific Session Crystal Ballroom, Hotel Whitcomb	4:30-5:30 p.m. ASSA Business Session Crystal Ballroom, Hotel Whitcomb
Sat. Oct. 25	8:00 a.m.-5:00 p.m. Registration ASSA, Mezzanine, Hotel Whitcomb 9:00-12 noon ASSA 2nd Scientific Session Crystal Ballroom, Hotel Whitcomb	Noon-2:00 p.m. ASSA Luncheon and G. L. Duff Lecture Corinthian Room, Hotel Whitcomb	2:00-5:00 p.m. AHA and ASSA Joint Panels on Arteriosclerosis Civic Auditorium	7:00-9:30 p.m. ASSA Members' Cocktails and Dinner Veneto's Restaurant
Sun. Oct. 26	9:00-12 noon ASSA 3rd Scientific Session Civic Auditorium		1:30-4:30 p.m. ASSA 4th Scientific Session President's Address (1:30:2 p.m.) Civic Auditorium	

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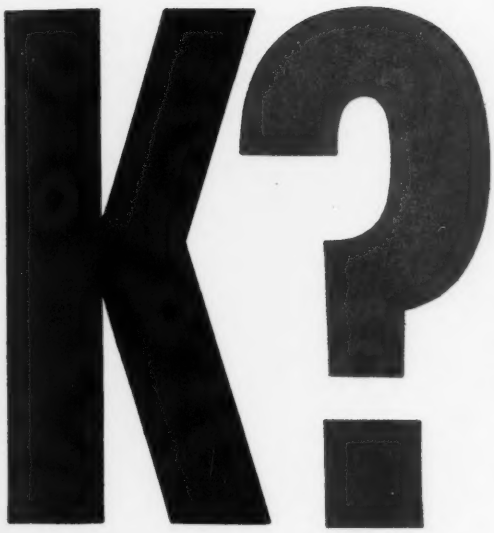
why all the fuss over potassium?



Many physicians will recall when safe but potent organomercurials were first introduced. At the time there was considerable worry about possible potassium loss. Patients were instructed to take foods rich in this mineral, and not infrequently potassium supplements also were advised. After enough experience was gained, it became evident that only the exceptional case could lose enough potassium to be concerned about. And with oral organomercurial diuretics this was practically never a problem.

Why revive the subject now? Because clinical experience with nonmercurial diuretics indicates most of them have such a specific effect on potassium that with their use very real problems must be faced. Enough potassium loss can lead to digitalis toxicity or to a classical overt hypopotassemia. Since a fair percentage of cardiacs who receive diuretics are also digitalized, this excess potassium excretion is clinically serious. Clinical experience is still too limited with some nonmercurial diuretics to say just how often such loss will occur—but warnings already have been sounded by some clinical investigators as to the need for potassium supplementation.

Experience in many patients, for many years, demonstrates that potassium loss is never a problem when NEOHYDRIN® is the oral diuretic. And there is no refractoriness to this effective oral organomercurial.

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